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# Determining the venous oxygen reservoir: A novel, hypothetical approach to titration of supplemental oxygen in preterm newborns

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A B S T R A C T

While *normal* oxygen saturation is commonly thought to be a marker of normal oxygenation, cutaneous saturation does not account for the sufficiency of oxygen within each cell or that of the system overall. Rather, cutaneous oximetry simply defines the saturation of haemoglobin (Hb) with oxygen in a pulsatile vessel. Assessment of sufficiency is best determined by measurement of the amount of oxygen *left over* following aerobic respiration. This *left over* oxygen is 'stored' on Hb in the venous compartment and can be calculated as the venous oxygen content. We hypothesize that the development of a venous oxygen content or saturation reference range in a group of well, uninjured very preterm newborns and subsequent application, in a randomised trial, with a structural, functional and molecular outcome will resolve the method for assessment of oxygen sufficiency in preterms by demonstrating both clinical safety and effectiveness. This method could be subsequently used for titration of supplemental oxygen.

## Introduction

Titration of supplemental oxygen is challenging in preterm newborns. This is despite a number of large, randomised, clinical trials designed to determine the effectiveness and safety of two alternate oxygen saturation target ranges on significant neonatal morbidity and mortality [1–6]. When combined, these trials suggest there is a tradeoff between both higher mortality and necrotising enterocolitis in newborns allocated to a low(er) oximetry target band (88–92%) compared with higher retinopathy of prematurity in newborns allocated to a relatively high(er) oximetry target band (91–95%). Thus, identification of a single Hb – oxygen saturation range that meets the oxygen requirements of all preterm newborns remains elusive.

Interrogating the general assumptions made regarding newborn oxygen requirements may help to understand why these clinical trials have been unable to reach agreement on a single saturation target. For example, all of the clinical trials of oxygen saturation targeting consider the enrolled newborn, in a comparable gestation based group, to have similar oxygen physiology at the time of treatment allocation. This ignores the possibility that oxygen physiology may in fact be independent of maturity. As each newborn baby likely has different oxygen physiology, at any particular time, this approach may in part explain the inconclusive results of the aforementioned clinical trials of titration of supplemental oxygen. By way of example, if cardiac output, Hb concentration and Hb oxygen saturation determine oxygen delivery [7] it is reasonably easy to imagine that a preterm newborn with poor cardiac output, low(er) Hb and Hb oxygen saturation has inferior oxygen delivery to a baby of similar maturity with high(er) cardiac output, Hb and saturation. In addition, factors known to influence oxygen consumption in the immediate newborn period include temperature [8,9], pulmonary disease [10], chorioamnionitis [11] and maternal $MgSO_4$ therapy [12]. Thus, each newborn has a slightly different combination of the constituent parts determining both oxygen delivery and consumption. For this reason, a summary measure of this relationship, independent of gestational age, is likely best able to determine overall oxygen system adequacy.

Exploring options that measure oxygen adequacy may also help to inform methods for titration of supplemental oxygen. Cutaneous measurement of oxygen saturation is most frequently used to assess newborn oxygen saturation, due to the ease and simplicity of application. However, this simply describes the saturation of haemoglobin (Hb) with oxygen in a pulsatile vessel and has many limitations [13]. Though many bedside staff consider normal saturation to be a marker of normal oxygenation, cutaneous saturation is an isolated measure of one of the constituent parts of oxygen delivery and does not account for the sufficiency of oxygen within each cell or that of the system overall. Rather,

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sufficiency is best determined by measurement of the amount of oxygen left over following aerobic respiration. This *left-over* oxygen is 'stored' on Hb in the venous compartment and is available for cellular metabolism through maintenance of the oxygen gradient between the blood and the cell.

The oxygen located in the venous compartment represents the difference between oxygen consumption and delivery. This quantity, termed the venous oxygen content, can be measured mathematically and includes Hb concentration, Hb – oxygen saturation and oxygen dissolved in the blood stream. Venous saturation solely describes the amount of oxygen on Hb within the venous compartment. It is in constant flux and differs within and between individuals as each has different oxygen delivery and consumption values at any one time. The difference between arterial and venous oxygen content is predominantly determined by Hb oxygen saturation as the Hb concentration is similar and the amount of oxygen dissolved in the blood stream is low. Thus, of available measures, the venous oxygen saturation likely provides the best dynamic measure of overall oxygen sufficiency in all but a few clinical conditions (e.g. derangement in cellular oxygen uptake).

Central venous oxygen status, whilst important, is very difficult to measure in the newborn. In place however, the oxygen status of the brain is typically the most informative particularly in the preterm baby as it is easy to standardise with clear landmarks and as an organ extremely sensitive to oxygen status is likely to act as a sentinel for overall system sufficiency. Here we describe the necessary steps for measuring venous oxygen saturation, as a dynamic surrogate for the venous oxygen content, in very preterm newborns and propose the design a trial of an alternate method for titrating oxygen in preterms so as to avoid harm from the consequences of both inadequate and excessive oxygen exposure.

## Objective

To develop an alternate method for assessing oxygen sufficiency in the preterm newborn that results in a reduction of harm from both excessive and inadequate oxygen exposure.

## Questions

Does titration of supplemental oxygen using a regional (cerebral) venous ($rcSO_2$) and cutaneous ($SaO_2$) oxygen saturation target band reduce the harm from excessive and inadequate oxygen exposure in preterm newborns?

## Specifically

i. Does measurement of cerebral oxygen kinetics, in well, very preterm newborns, provide an operational reference range for the venous oxygen content and venous oxygen saturation?
ii. Does application of an alternate method for assessment of oxygen sufficiency, using both venous oxygen saturation and cutaneous oxygen saturation reduce the harm from the consequences of both excessive and inadequate oxygen exposure?

## Background

Oxygen kinetics varies in every newborn, with each having subtly different oxygen delivery and consumption. For this reason, neither delivery nor consumption alone characterises the overall status of the oxygen physiologic relationship. Oxygen delivery and consumption are in constant flux depending on both endogenous (activity) and exogenous factors (environmental temperature). At rest, oxygen delivery is sufficiently greater than consumption resulting in aerobic conditions with a significant amount of oxygen left over in the venous oxygen compartment. As oxygen delivery falls, consumption increases or both occur in combination, the amount of oxygen extracted from Hb increases, thus reducing the amount left over on Hb located in the venous oxygen compartment (venous oxygen saturation). Eventually, as oxygen consumption exceeds delivery, the venous oxygen compartment is drained resulting in anaerobic respiration and the accumulation of lactate. This process has been functionally demonstrated in a small, randomised study in stable, ventilated preterm newborns in whom inspired oxygen concentration was adjusted to achieve two different targets, either 91–94% or 95–98% [14]. Within the lower saturation group, both arterial oxygen content and required inspired oxygen tension fell with no change in oxygen consumption. This indicates that newborns increase the amount of oxygen extracted from Hb in response to lower arterial oxygen content by accessing the store of oxygen that would otherwise be located in the venous compartment.

Oxygen extraction is a calculated variable that quantifies the amount of oxygen unloaded from haemoglobin [7]. The process of extraction is dependent on the establishment and maintenance of an oxygen gradient from the alveolar–pulmonary capillary interface to the cell [7]. Thus, extraction functions as a system buffer temporarily offsetting shortfalls of oxygen delivery or brief rises in consumption. As extraction increases, the amount of oxygen left on Hb located in the venous oxygen compartment falls until a value is reached beyond which lactic acidosis develops. Animal models have shown that the critical venous oxygen level at which anaerobic metabolism develops is slightly different in stagnant (low flow) compared with anaemic (low Hb) and hypoxic (low inspired oxygen concentration) hypoxia [15–17]. It is unclear if a similar pattern is observed in preterm newborns in whom a mixed model of hypoxaemia is most typical. Further, the small amount of oxygen located in the venous compartment that is unavailable even when maximal compensation is required, likely reflecting the minimum obligatory oxygen gradient between the blood stream and mitochondrion, has not been defined in human newborns.

Near Infra-red Spectroscopy (NIRS) is a validated method for measurement of tissue oxygen bound to Hb [18]. It is based on spectrometric measurement of oxygen dependent changes in the absorption properties of the chromophores, haemoglobin and cytochrome aa3, in the near infra-red range. Previous researchers have described reference ranges for cortical tissue oxygen levels in preterm newborns. In the largest study, Alderliesten measured cortical (venous) tissue oxygen in the first three days of life, using a variety of NIRS devices (with neonatal and adult sensors) in a population of newborns from 24 up to 32 weeks [19]. This study showed a wide range of values, with all increasing with gestational and chronologic age. For example, the 10th, 25th, 50th, 75th and 90th centile for cerebral (venous) tissue saturation ($rSO_2$) in the first 12 h of life in preterm infants born at 24–25 weeks' gestation is 52%, 57% 62%, 70 and 72%. Whilst this study is very informative, there are a number of limitations, in particular, the use of heterogeneous NIRS devices, non standardisation of cutaneous saturation and inclusion of newborns with and without injury.

The SafeBOOSc trial of NIRS derived cerebral $rSO_2$ targeting included 166 babies born less than 28 weeks' gestation who were less than 3 h of age [20]. Newborns were randomised to either standard care, with inspired oxygen concentration titrated using cutaneous oximetry and a NIRS device applied, but not visible, or, alternately, to an intervention arm incorporating a combination of NIRS derived cerebral $rSO_2$ target and treatment guideline. The intervention arm was designed with a treatment guideline, based on therapies targeting oxygen delivery, to help clinical staff manage babies within a cerebral $rSO_2$ target of 55–85%. This target was based on unpublished data from 439 preterm newborns < 32 weeks' gestation. Cumulative time and distance (depth) from the reference range (area under the curve) were used as primary outcomes. This clinical trial provides clear evidence that an alternate model of oxygen titration using NIRS derived cerebral $rSO_2$ is possible in a newborn intensive care setting. Unfortunately however, there was no hierarchy to the respiratory and circulatory treatment guideline; rather an intervention was solely determined by