A Model Analysis of Arterial Oxygen Desaturation during Apnea in Preterm Infants

Scott A. Sands¹, Bradley A. Edwards¹, Vanessa J. Kelly¹, Malcolm R. Davidson², Malcolm H. Wilkinson¹, Philip J. Berger¹*

¹Ritchie Centre for Baby Health Research, Monash Institute of Medical Research, Monash University, Victoria, Australia, ²Department of Chemical and Biomolecular Engineering, Faculty of Engineering, University of Melbourne, Victoria, Australia

Abstract

Rapid arterial O₂ desaturation during apnea in the preterm infant has obvious clinical implications but to date no adequate explanation for why it exists. Understanding the factors influencing the rate of arterial O₂ desaturation during apnea (SSaO₂) is complicated by the non-linear O₂ dissociation curve, falling pulmonary O₂ uptake, and by the fact that O₂ desaturation is biphasic, exhibiting a rapid phase (stage 1) followed by a slower phase when severe desaturation develops (stage 2). Using a mathematical model incorporating pulmonary uptake dynamics, we found that elevated metabolic O₂ consumption accelerates SSaO₂ throughout the entire desaturation process. By contrast, the remaining factors have a restricted temporal influence: low pre-apneic alveolar P₀₂ causes an early onset of desaturation, but thereafter has little impact; reduced lung volume, hemoglobin content or cardiac output, accelerates SSaO₂ during stage 1, and finally, total blood O₂ capacity (blood volume and hemoglobin content) alone determines SSaO₂ during stage 2. Preterm infants with elevated metabolic rate, respiratory depression, low lung volume, impaired cardiac reserve, anemia, or hypovolemia, are at risk for rapid and profound apneic hypoxemia. Our insights provide a basic physiological framework that may guide clinical interpretation and design of interventions for preventing sudden apneic hypoxemia.

Introduction

Apnea and its accompanying arterial O₂ desaturation are common clinical complications in preterm infants, occurring in more than 50% of very low birth weight infants [1]. In preterm infants, apnea causes a reduction in heart rate [2] and cerebral perfusion [3], often requires mechanical ventilation, and is associated with neurodevelopmental impairment [4]. Apnea-related hypoxemia is of major concern in light of evidence that repetitive hypoxia in newborn animals results in irreversibly-altered carotid body function [3], raising the possibility of impaired ventilatory control, and causes neurocognitive and behavioural deficits [6]. Respiratory arrest and hypoxemia are also strongly implicated in sudden infant death syndrome (SIDS) [7,8] where the speed at which hypoxemia develops is considered to be particularly dangerous.

In preterm infants, the rate of arterial O₂ desaturation (SSaO₂) can be highly variable and rapid, with average rates as high as 4.3% s⁻¹ during isolated apneas [9]. An earlier framework to describe SSaO₂ proposed that metabolic O₂ consumption relative to alveolar volume determines the speed at which alveolar P₀₂ falls [10]; it was envisaged that SSaO₂ is then a function of falling P₀₂ and the slope of the oxy-hemoglobin dissociation curve. However, such a model assumes that the rate of alveolar depletion of O₂, denoted pulmonary O₂ uptake (VVpO₂), is equal to tissue O₂ consumption during apnea (see Methods – Theory). Previous studies in adults have shown that VVpO₂ falls from metabolic consumption during apnea [11], and our previous modeling studies in lambs showed that the difference between VVpO₂ and metabolic O₂ consumption has a crucial role in determining SSaO₂ during recurrent apneas [12]. We found that apneic changes in VVpO₂ cause desaturation to occur in 2 stages. During stage 1, lung O₂ stores are depleted, and VVpO₂ falls below metabolic consumption. During stage 2, VVpO₂ is close to zero, and tissue O₂ needs are provided by depletion of blood O₂ stores.

To date, no complete theoretical analysis of the factors influencing desaturation during apnea has been published. The only available study [13] has a number of critical limitations. First, the model incorporated a constraint of a fixed difference between SSaO₂ and mixed-venous saturation; thus dynamic changes in VVpO₂ could not occur and their influence on SSaO₂ could not be examined. Second, no assessment was made of the impact of cardiorespiratory factors on the two stages of O₂ desaturation. Third, in focusing on adults, the study did not examine profound desaturation to levels well below 60% as can often occur in preterm infants [9,14].

Accordingly, the aim of the current study was to quantify the importance of cardiorespiratory factors relevant to SSaO₂ during apnea, with particular reference to the preterm infant. Using a model that permits variation of VVpO₂ during apnea, we examine a number of factors known to influence SSaO₂, such as lung volume [15], metabolic O₂ consumption [16] and pre-apneic arterial oxygenation [17] as well as factors that are particularly pertinent for...
the developing newborn, including anemia, hypovolemia, reduced $O_2$ affinity, and chronically and acutely reduced cardiac output. We use the results to develop a conceptual framework for the interpretation of mechanisms underlying rapid $SSaO_2$ during apnea.

**Results**

**Overview of the two-compartment model for gas exchange**

To determine the independent influence of clinically relevant cardiorespiratory factors on $SSaO_2$, during a single isolated apnea, we used a two-compartment lung-body mathematical model which incorporated realistic blood $O_2$ stores and gas exchange dynamics (Figure 1), as described in Methods – Mathematical model (a full list of symbols is provided in Table 1). We used published parameters for healthy preterm infants born at ~30 wk gestational age (Table 2); the values represent measurements taken at approximately term equivalent age when surprisingly rapid desaturation has been observed [9]. We also derive analytic solutions for $SSaO_2$ to quantify the importance of cardiorespiratory factors on $SSaO_2$ to obtain a detailed view of the arterial $O_2$ desaturation process, as described in Methods – Theory.

**Pulmonary gas exchange dynamics during apnea**

To examine changes in $O_2$/$CO_2$ exchange during apnea, a single apnea was imposed on the model. During apnea, changes in alveolar $O_2$ and $CO_2$ stores are not constant (Figure 2); importantly, alveolar $P_{O_2}$ ($P_{AO_2}$) did not continue to fall at its initial rate as governed by metabolic $O_2$ consumption ($VV_{pO_2}$), but instead the rate of fall in $P_{AO_2}$ was reduced as it approached mixed venous $P_{O_2}$ ($PP_{O_2}$), an observation also reflected in the falling $VV_{pO_2}$ as a result, two distinct phases for $O_2$ depletion can be seen, which we refer to as stage 1 and stage 2 [12]. During stage 1, $P_{AO_2}$ fell rapidly and $VV_{pO_2}$ decreased and became dissociated from $VV_{pO_2}$; during stage 2, with $VV_{pO_2}$ greatly reduced, both $P_{AO_2}$ and $PP_{O_2}$ fell together at a reduced rate. The two distinct phases were also observed for alveolar and arterial $P_{CO_2}$ ($P_{ACO_2}$, $P_{ACO_2}$) although stage 1 for $CO_2$ was substantially shorter than that for $O_2$. Such an effect results from the earlier fall in pulmonary $CO_2$ uptake ($VV_{pCO_2}$) relative to the fall in $VV_{pO_2}$ (Figure 2A) and is reflected in the reduction in respiratory exchange ratio ($VV_{pCO_2}/VV_{pO_2}$) (Figure 2B). Consequently, a more rapid fall in $P_{AO_2}$ was observed compared with the rise in $P_{ACO_2}$(see Methods – Derivation of equations), such that $P_{AO_2}$ fell by 100 mmHg in the time $P_{ACO_2}$ rose by just 14 mmHg (Figure 2C).

**Time-course of $SSaO_2$ during apnea**

The time-course of $SSaO_2$ is complex (Figure 3), a consequence of the nonlinear $O_2$-dissociation curve in combination with the fall in $VV_{pO_2}$. At apnea onset, $SSaO_2$ started to fall with a rate equivalent to that predicted by Equation 12, where $SSaO_2 = 0.5\%s^{-1}$ (Figure 3). During apnea, changes in the slope of the $O_2$-dissociation curve ($\beta_{HbO_2}$) and $VV_{pO_2}$ dominated the time-course of desaturation as hypoxemia progressed. As $SSaO_2$ started to fall after apnea onset, $\beta_{HbO_2}$ increased with little change in $VV_{pO_2}$, resulting in a proportional increase in $SSaO_2$. However, as arterial hypoxemia developed, there was a concurrent decline in $VV_{pO_2}$. As $SSaO_2$ is directly proportional to the product $\beta_{HbO_2} \times VV_{pO_2}$ (Equation 11) it follows that during apnea, the peak $SSaO_2$ of 3.5\%s^{-1} occurred when $\beta_{HbO_2} \times VV_{pO_2}$ reached a maximum. This occurred when neither $VV_{pO_2}$ nor $\beta_{HbO_2}$ was at its maximum (both ~50\% of peak). Finally, with $VV_{pO_2}$ greatly reduced during stage 2, $SSaO_2$ remained at a constant level ($SSaO_2 = 1.7\%s^{-1}$, close to that predicted by Equation 13 (1.8\%s^{-1})).

**Factors influencing $SSaO_2$**

The following parameters were individually varied from their ‘normal’ values to quantify their influence on $SSaO_2$: resting $P_{AO_2}$,
Factors Influencing Rapid Arterial $O_2$ Desaturation

To quantify $S_{aO_2}$, we used 3 different measures. First, since apnea is considered clinically significant if it lasts for >10 s and is accompanied by bradycardia or $O_2$ desaturation [18], we calculated the average rate of fall in $S_{aO_2}$ between apnea onset and 10 s later ($S_{aO_2}^{10\text{~s}}$) such a measure describes the immediacy of onset of desaturation and is analogous to the practical measurement of average $S_{aO_2}$ used in many clinical studies [9,15,19,20]. Second, we determined the peak instantaneous $S_{aO_2}$ during apnea

Table 1. Mathematical symbols.

| Symbol | Description |
|--------|-------------|
| $C_{aCO_2}$ | Arterial $CO_2$ content |
| $C_{aO_2}$ | Arterial $O_2$ content |
| $C_{vCO_2}$ | End-capillary arterial $CO_2$ content |
| $C_{vO_2}$ | End-capillary arterial $O_2$ content |
| $C_{vO_2}$ | Mixed venous $O_2$ content |
| $C_{vCO_2}$ | Rate of change in mixed venous $CO_2$ content |
| $C_{vO_2}$ | Rate of change in mixed venous $O_2$ content |
| $F_{I O_2}$ | Fractional inspired $O_2$ |
| $F_S$ | R-L pulmonary shunt fraction ($Q_T/Q_L$) |
| $Hb$ | Hemoglobin content of blood |
| $P_0$ | Barometric pressure, including conversion from STP to BTP, 863 mmHg |
| $P_{50}$ | $O_2$ partial pressure at 50% saturation |
| $P_{O_2}$ | $O_2$ partial pressure |
| $P_{ACO_2}$ | Arterial $CO_2$ partial pressure |
| $P_{A}O_2$ | Arterial $O_2$ partial pressure |
| $P_{A}CO_2$ | Alveolar $CO_2$ partial pressure |
| $P_{A}O_2$ | Alveolar $O_2$ partial pressure |
| $P_{aO_2}$ | Alveolar $O_2$ partial pressure |
| $P_{a}CO_2$ | Alveolar $CO_2$ partial pressure |
| $P_{exp}$ | Alveolar water vapour partial pressure, 47 mmHg |
| $P_{a}$ | Barometric pressure, 760 mmHg |
| $P_{C}CO_2$ | End-capillary $CO_2$ partial pressure |
| $P_{C}O_2$ | End-capillary $O_2$ partial pressure |
| $P_{I}CO_2$ | Inspired $CO_2$ partial pressure |
| $P_{I}O_2$ | Inspired $O_2$ partial pressure |
| $P_{V}CO_2$ | Mixed venous $CO_2$ partial pressure |
| $P_{V}O_2$ | Mixed venous $O_2$ partial pressure |
| $P_{A}O_2$ | Rate of change in alveolar $O_2$ partial pressure |
| $P_{A}CO_2$ | Rate of change in alveolar $CO_2$ partial pressure |
| $P_{A}O_2$ | Rate of change in alveolar $O_2$ partial pressure |
| $Q_a$ | Arterial volume |
| $Q_{bO_2}$ | Blood volume for $O_2$ |
| $Q_{bCO_2}$ | Blood volume for $CO_2$ |
| $Q_{v}$ | Venous (and tissue) volume |
| $Q_{vCO_2}$ | Venous (and tissue) volume for $CO_2$ |
| $Q_{vO_2}$ | Venous (and tissue) volume for $O_2$ |
| $Q_{T}$ | Cardiac output |
| $Q_{P}$ | Pulmonary blood flow |
| $R_{ER}$ | Respiratory exchange ratio ($V_{P_{C}O_2}/V_{P_{A}O_2}$) |
| $S_{O_2}$ | $O_2$ saturation |
| $S_{aO_2}$ | Arterial $O_2$ saturation |
| $S_{C_{aO_2}}$ | End-capillary arterial $O_2$ saturation |
| $S_{V}O_2$ | Mixed venous $O_2$ saturation |
| $S_{aCO_2}$ | Rate of arterial $CO_2$ desaturation |
| $S_{aO_2}^{10\text{~s}}$ | Average $S_{aO_2}$ from t=0–10 s during apnea |

$P_{O_2}$ is the partial pressure at 50% saturation. $V_l$ is taken from data on functional residual capacity. For all simulations unless otherwise stated: respiratory exchange ratio (RER) was assumed to be 0.8, shunt fraction ($F_S$) was adjusted to 8.7% to achieve a resting $P_{aO_2}$ of 72 mmHg as is typical for normal healthy infants [58]; resting alveolar ventilation ($V_I$ = 168 ml min$^{-1}$ kg$^{-1}$ under normal conditions) was set to achieve resting $P_{aCO_2}$ = 100 mmHg.

doi:10.1371/journal.pcbi.1000588.t002

Table 2. Typical parameters for the preterm infant at term equivalent age.

| Parameter | Value | Reference/s |
|-----------|-------|-------------|
| Lung volume ($V_l$) | 20 ml kg$^{-1}$ | [31,54] |
| Metabolic $O_2$ consumption ($V_{O_2}$) | 10 ml min$^{-1}$ kg$^{-1}$ | [55,39,40] |
| Cardiac output ($Q_T$) | 250 ml min$^{-1}$ kg$^{-1}$ | [56] |
| Hemoglobin content (Hb) | 8 g dL$^{-1}$ | [22] |
| $P_{O_2}$ | 24 mmHg | [22] |
| Blood volume ($Q_b$) | 80 ml kg$^{-1}$ | [57] |

doi:10.1371/journal.pcbi.1000588.t001
Factors Influencing Rapid Arterial O₂ Desaturation

Figure 2. Pulmonary gas exchange during apnea. (A) Rate of pulmonary O₂/CO₂ exchange. V̇₉₀ and V̇₁₉₀, fall from resting levels during apnea. (B) Net alveolar-capillary gas uptake (V̇p₉₀ = V₉₀ – V₁₉₀) and respiratory exchange ratio (ṘER = V̇₁₉₀/V̇₉₀) during apnea. (C) Changes in alveolar, arterial and mixed venous P₉₀/P₇₀ during apnea. Contrast the time-course in P₉₀ and P₇₀ as they fall/rise towards P₉₀/P₇₀. (*) represents the fall in P₉₀ if V₉₀ was assumed equal to V̇₉₀. S1 = stage 1; S2 = stage 2. doi:10.1371/journal.pcbi.1000588.g002

Figure 3. The time course of Š₉₀ during apnea. Panel (A) shows the increase in the slope of the oxy-hemoglobin dissociation curve at the level of alveolar P₉₀ (lHb₉₀), and the fall in pulmonary oxygen uptake (V₉₀) that occurs during apnea. Panel (B) shows that changes in the product lHb₉₀ × V₉₀ explain the time course of the instantaneous slope of arterial O₂ desaturation (SAO₂) during apnea. Note that the peak SAO₂ occurs when V₉₀ is substantially less than its resting value. Note also that the rate of fall of mixed-venous saturation (SV₀₂) and SAO₂ become equal and constant after 20 s. doi:10.1371/journal.pcbi.1000588.g003

Figure 4. Alveolar-capillary gas exchange during apnea. (A) Rate of alveolar gas exchange. V̇₉₀ and V̇₁₉₀ fall from resting levels during apnea. (B) Net alveolar-capillary gas uptake (V̇p₉₀ = V₉₀ – V₁₉₀) and respiratory exchange ratio (ṘER = V̇₁₉₀/V̇₉₀) during apnea. (C) Changes in alveolar, arterial and mixed venous P₉₀/P₇₀ during apnea. Contrast the time-course in P₉₀ and P₇₀ as they fall/rise towards P₉₀/P₇₀. (*) represents the fall in P₉₀ if V₉₀ was assumed equal to V̇₉₀. S1 = stage 1; S2 = stage 2. doi:10.1371/journal.pcbi.1000588.g002

Table 3. Impact ratios describing the effect of cardiorespiratory factors on SAO₂.

| Parameter alteration | SAO₂³⁰⁺ | SAO₂peak | SAO₂stage 2 |
|----------------------|---------|----------|------------|
| Resting PA₉₀         | -3.97   | -0.35    | -0.01      |
| Lung volume (Vl)     | -2.24   | -0.82    | -0.09      |
| Blood volume (Qb)    | -0.01   | -0.06    | -0.68      |
| O₂ consumption (V₉₀)  | +2.29   | +1.00    | +1.00      |
| O₂ consumption (V₉₀)  | +2.73   | +1.92    | +1.00      |
| Hemoglobin content (Hb) ³ | -0.38   | -1.00    | -0.89      |
| Hemoglobin content (Hb) ⁴ | +0.01   | -0.10    | -0.89      |
| P₉₀                 | +1.37   | -0.68    | -0.11      |
| Cardiac output (Ql, resting) | -0.39   | -0.90    | 0.00       |
| Cardiac output (Ql, transient) | +1.45   | -0.06    | 0.00       |
| Shunt Fraction (Fs)  | -0.01   | +0.01    | 0.00       |

Impact ratio is defined as the ratio of proportional increase in SAO₂ to the proportional increase in each factor, based on small changes around normal values. An impact ratio of 1 indicates a one-to-one increase in SAO₂ with an increase in the factor, and a negative ratio indicates an inverse relationship. CC = cardiac compensated, nCC = cardiac uncompensated. doi:10.1371/journal.pcbi.1000588.t003

Additionally, a severe reduction in SAO₂ causes a 6% reduction in the resting and respiratory exchange ratio (ṘER = V̇₁₉₀/V̇₉₀) during apnea. This occurs despite only a minor influence being visible on resting SAO₂. For example, a reduction of P₉₀ from 100 to 60 mmHg caused a 6% reduction in resting SAO₂ but at the same time led to a more than 2-fold elevation in SS₉₀ during apnea (Figure 4B). Additionally, a severe reduction in P₆₉₀, to below 70 mmHg, was required to elevate SS₉₀.
1 desaturation as reflected in no change in $\dot{S}_{\text{aO}_2}^{\text{peak}}$ or $\dot{S}_{\text{aO}_2}^{10s}$ (Figure 6A, B).

**Metabolic O$_2$ consumption ($\dot{V}O_2$).** To examine the impact of changing $\dot{V}O_2$ on $\text{SaO}_2$, independent of resting $\dot{SV}_{\text{O}_2}$, $\dot{Q}T$ was adjusted to maintain resting $\text{SaO}_2$ constant, where $\Delta QT(\%) = \Delta \dot{V}O_2(\%)$; we refer to this procedure as ‘cardiac compensation’. Under this condition, elevated $\dot{V}O_2$ caused a directly proportional increase in $\text{SaO}_2$ throughout stages 1 and 2 (Figure 6A, B). Without cardiac compensation, the effect of increased $\dot{V}O_2$ on $\text{SaO}_2$ during stage 1 was magnified, as shown by the further increase in $\dot{S}_{\text{aO}_2}^{\text{peak}}$ (Figure 6A, B).

**Hemoglobin content (Hb) and oxygen affinity ($P_{50}$).** Reduced hemoglobin content (Hb) increased $\text{SaO}_2$ and $\dot{S}_{\text{aO}_2}^{10s}$ but had little effect on $\dot{S}_{\text{aO}_2}^{\text{peak}}$ (Figure 7A, B). The increase in $\text{SaO}_2$ occurred with an increase in the peak of the product $\beta HbO_2 \times VPO_2$, as $VPO_2$ was higher at each level of $\dot{V}O_2$. The simulation was repeated with cardiac compensation for the reduction in hemoglobin content, where $\Delta QT(\%) = 1/\Delta Hb(\%)$, to maintain constant resting $\text{SaO}_2$. Following such compensation, no changes in $\dot{S}_{\text{aO}_2}^{\text{peak}}$ or $\dot{S}_{\text{aO}_2}^{10s}$ were observed but reduced Hb continued to increase $\dot{S}_{\text{aO}_2}^{\text{stage} 2}$. In examining the influence of $P_{50}$, $P_{90}$ was adjusted in equal proportion on the basis of published data [22]. Increased $P_{90}$ increased the immediate $\text{SaO}_2$, increased $\dot{S}_{\text{aO}_2}^{10s}$, decreased $\dot{S}_{\text{aO}_2}^{\text{peak}}$ and had no effect on $\dot{S}_{\text{aO}_2}^{\text{stage} 2}$ (Figure 7C, D).

**Cardiac output ($\dot{Q}T$).** Reduced resting $\dot{Q}T$ increased $\dot{S}_{\text{aO}_2}^{\text{peak}}$, but had little impact on $\dot{S}_{\text{aO}_2}^{10s}$ or $\dot{S}_{\text{aO}_2}^{\text{stage} 2}$ (Figure 8A, B). As with Hb, the increase in $\dot{S}_{\text{aO}_2}^{\text{peak}}$ with reduced resting $\dot{Q}T$ occurred with an increase in the peak of the product $\beta HbO_2 \times VPO_2$. To differentiate between the influence on $\text{SaO}_2$ of an acute reduction in cardiac output, i.e. when bradycardia accompanies apnea, rather than a chronic reduction, we reduced cardiac output in a step-wise manner from the baseline value at the time of apnea onset. In contrast to the effect of reduced resting $\dot{Q}T$, a transient reduction in $\dot{Q}T$ decreased $\dot{S}_{\text{aO}_2}^{10s}$ but had a negligible impact on $\dot{S}_{\text{aO}_2}^{\text{peak}}$, or $\dot{S}_{\text{aO}_2}^{\text{stage} 2}$ (Figure 8C, D).

**Resting R-L shunt fraction ($F_S$).** Increased $F_S$ reduced resting $\text{SaO}_2$ and $\dot{SV}_{\text{O}_2}$ but had no effect on $\dot{S}_{\text{aO}_2}^{10s}$, $\dot{S}_{\text{aO}_2}^{\text{peak}}$, or $\dot{S}_{\text{aO}_2}^{\text{stage} 2}$ (Figure 9A, B).

**Discussion**

Our model analysis of the rate of arterial O$_2$ desaturation during apnea demonstrates that pre-apneic ventilation, lung volume, cardiac output, hemoglobin content and blood volume exert unique effects on $\dot{S}_{\text{aO}_2}$ throughout the time-course of desaturation, while metabolic O$_2$ consumption is uniformly influential throughout the process. Our analysis reveals that lung volume and the slope of the O$_2$-dissociation curve are important early in the process, during what we refer to as stage 1 [12], but not stage 2. For the first time, our study reveals that reduced cardiac output and hemoglobin content, and as a consequence resting mixed-venous saturation, substantially accelerate peak $\dot{S}_{\text{aO}_2}$. Finally, low blood volume and hemoglobin content, and therefore a low total blood O$_2$ capacity, increase the speed of desaturation, but only in stage 2. In addition to infants with elevated metabolic needs and low lung volume, those with anemia, cardiac dysfunction, or hypovolemia, which are common complications of prematurity, are at heightened risk of rapid and profound arterial desaturation during apnea.

**Methodological considerations**

To evaluate the independent effects of cardiorespiratory factors on $\dot{S}_{\text{aO}_2}$ we used a two-compartment model, incorporating both alveolar and blood gas stores. The inclusion of a realistic blood store was crucial to reveal that changes in $VPO_2$ occur as a consequence of arterial and mixed-venous saturation falling...
asynchronously during apnea (Figure 3). Our approach allowed us to extend the previous framework based on the assumption of constant \( V_{\text{P}O_2} \) [23], which prevented the recognition that a steep \( O_2 \)-dissociation curve and low lung volume do not accelerate \( \dot{S}_{\text{A}O_2} \) beyond stage 1. Furthermore, the varying \( V_{\text{P}O_2} \) permitted recognition that cardiac output, hemoglobin content, and blood volume have a major influence on \( \dot{S}_{\text{A}O_2} \).

In the current study, the typical value of \( \dot{S}_{\text{A}O_2} \) found using our model was 3.5% s\(^{-1}\) whereas Poets and Southall [9] using beat-by-beat oximetry in preterm infants reported a mean value for \( \dot{S}_{\text{A}O_2} \) of 4.3% s\(^{-1}\) during isolated apneas. Reasons for our lower value may lie with our simplifying assumptions. Notably, we assumed a homogenous lung compartment and complete gas mixing and as such, the model incorporated neither limitation of alveolar-capillary diffusion nor an uneven ventilation-perfusion distribution, two factors that could cause an increase in \( \dot{S}_{\text{A}O_2} \). In addition, we assumed a constant lung volume during apnea, equal to published values of functional residual capacity, whereas it is known that lung volume can fall during apnea [15,24]; based on our data, a fall in lung volume to 15.5 ml kg\(^{-1}\) immediately after apnea onset would achieve \( \dot{S}_{\text{A}O_2} \) of 4.3% s\(^{-1}\) (Figure 5B).

A final assumption implicit in our model is that all \( O_2 \) transfer to the blood occurs via the pulmonary circulation. However, in very preterm infants there is evidence of cutaneous respiration in the first few days of life in both room air and with supplemental \( O_2 \) [25]. With whole body exposure of 90% \( O_2 \) to the newborn skin, it
has been calculated that $\dot{V}_{\text{PO}_2}$ can be reduced by 8–10% [26], likely via an increased resting mixed-venous saturation; our study demonstrates that such an effect would decrease $S_aO_2$ during apnea.

### Pulmonary gas exchange dynamics during apnea

Our study is consistent with previous observations that $\dot{V}_{\text{PO}_2}$ and $\dot{V}_{\text{PCO}_2}$ rapidly decline during apnea from their steady-state values [11], with $\dot{V}_{\text{PCO}_2}$ falling faster than $\dot{V}_{\text{PO}_2}$. The relatively low blood capacitance for $O_2$ compared with that for $CO_2$ results in the resting alveolar–mixed-venous partial pressure difference being ~12-fold greater for $O_2$ than for $CO_2$. Consequently, when apnea begins ~12 times more $O_2$ than $CO_2$ must diffuse across the lung to obliterate the alveolar–mixed-venous partial pressure difference. The slower fall in $\dot{V}_{\text{PO}_2}$ vs. $\dot{V}_{\text{PCO}_2}$ provides for a faster depletion of alveolar $O_2$ vs. $CO_2$ stores; such an effect results in complete desaturation of arterial blood in the time $P_{\text{ACO}_2}$ rises by just 14 mmHg. These findings lead us to conclude that short-term $O_2$ homeostasis is more unstable than $CO_2$ homeostasis and thus that the danger of isolated apneas in infants is likely to be mediated via hypoxemia rather than hypercapnia.

### Factors influencing $S_aO_2$

Our study provides for the first time a comprehensive analysis of the factors that determine arterial desaturation during apnea in preterm infants. We show that resting oxygenation in the form of alveolar $P_{O_2}$ has the greatest influence on desaturation at apnea onset. When apnea begins at an increasingly lower alveolar $P_{O_2}$, $S_aO_2$ more quickly reaches its maximum because $P_{O_2}$ rapidly arrives at the steepest part of the $O_2$-dissociation curve. This effect explains the inverse relationship between mean $S_aO_2$ and pre-apneic $S_aO_2$ during apnea [17], but as we show the peak slope itself is negligibly affected by reduced resting $P_{O_2}$ within the normal range.

We demonstrate that $S_aO_2$ is inversely related to lung volume during stage 1 of apnea as a result of the greater reduction in alveolar $P_{O_2}$ in poorly inflated lungs per unit of $O_2$ transferred into the pulmonary capillaries. This analysis is consistent with the inverse correlation between $S_aO_2$ and lung volume [13], with the view that active upper airway closure maintains lung volume and slows $S_aO_2$ [27,28], and with our recent report that the application of continuous positive airway pressure effectively slows $S_aO_2$ in lambs [29]. However, once stage 2 begins, the blood becomes the principal source of $O_2$ and thus the only store which influences $S_aO_2$.

A novel finding from our study is that reduced resting mixed-venous saturation, caused by either a reduced cardiac output or reduced hemoglobin content, strongly elevates peak $S_aO_2$, independent of metabolic $O_2$ consumption. We show that reduced resting mixed-venous saturation accelerates $S_aO_2$ via an increase in the peak value of $\dot{SH}_bO_2 \times \dot{V}_{PO_2}$; in other words, low mixed-venous saturation provides for a greater pulmonary $O_2$ uptake even in the presence of a developing arterial hypoxemia, and thereby increases $S_aO_2$. A role for hemoglobin in determining $S_aO_2$ is consistent with the finding that elevated hemoglobin content in adults slows $S_aO_2$ during apnea [21]. In contrast, blood transfusion to raise hemoglobin content in anemic preterm infants, a common clinical therapy, has little or no impact on the severity of apneic desaturation [30]. Our proposed explanation for the lack of benefit of raising hemoglobin content via transfusion is that it also reduces heart rate [30] and cardiac output. Thus, in the newborn, the rise in mixed-venous saturation expected after transfusion is counteracted by a tendency for mixed-venous saturation to fall as a result of reduced cardiac output. An investigation that failed to find an effect of cardiac output on $S_aO_2$ [23] did not account for our
finding that pre-apneic and transient changes in cardiac output have opposing influence on $\text{SSaO}_2$. Importantly, we find that a transient fall in cardiac output, characteristic of bradycardia during apnea in preterm infants [2], conserves alveolar O2 via reduced $\text{VVpO}_2$ and thus reduces $\text{SSaO}_2$ (see Equations 10 and 11). Consistent with this finding, apneic bradycardia prevents a rapid fall in $\text{SaO}_2$ in adults [21].

We found that each of the factors examined exerts a unique and therefore recognisable influence on the time course of the desaturation process (Figure 10). Low alveolar $\text{P}_\text{O}_2$ can be recognised by a left-shift of the desaturation trajectory so that desaturation begins sooner following the onset of apnea. A steep desaturation slope in the early phase of stage 1 points to a low ratio of lung volume to metabolic O2 consumption. In the late phase of stage 1, when desaturation proceeds in a linear fashion, a low resting mixed-venous saturation accelerates $\text{SaO}_2$ and leaves the fingerprint of a low inflection point in arterial $\text{O}_2$ desaturation; low resting mixed-venous saturation reflects low cardiac output or hemoglobin content with respect to O2 consumption. Lastly rapid $\text{SaO}_2$ during stage 2 signifies a low total blood O2 capacity with respect to O2 consumption which would point to either low blood volume or anemia. The presence of a constant R-L shunt, while having no influence on $\text{SSaO}_2$, causes a parallel downwards shift in the desaturation trajectory. The unique impact of different factors on the desaturation curve may be used to guide preventive clinical intervention.

Figure 7. Impact of hemoglobin content (Hb) and O2 affinity ($P_{50}$) on $\text{SSaO}_2$. (A) Effect of three levels of Hb, (i) 12 g dL$^{-1}$, (ii) 8 g dL$^{-1}$ and (iii) 4 g dL$^{-1}$, on arterial ($\text{SaO}_2$) and mixed venous ($\text{SVV}_2$) O2 desaturation during apnea. Note the fall in $\text{SaO}_2$ at the inflection point (shown by short black lines). Note also that the reduced Hb has little impact on desaturation above $\text{SaO}_2 \approx 80\%$. (B) Sensitivity of $\text{SSaO}_2$ to changes in Hb. (C) Effect of three levels of $P_{50}$, (iv) 18 mmHg, (v) 24 mmHg, and (vi) 36 mmHg, on $\text{SSaO}_2$. (D) Sensitivity of $\text{SSaO}_2$ to changes in $P_{50}$. $n$ = ‘normal’ values; S1, stage 1 slope; S2, stage 2 slope.

doi:10.1371/journal.pcbi.1000588.g007
Clinical significance

We show theoretically that the lower lung volume [31] and higher metabolic O2 consumption [32] of preterm compared to term infants predisposes to a rapid onset and progression of desaturation during apnea. Two reports offer support for this view. First, rapid desaturation occurs in infants with low functional residual capacity [15], a finding that may help to explain the more frequent O2 desaturation events during active sleep [33] when functional residual capacity is reduced. Second, frequent desaturation is characteristic of preterm infants with bronchopulmonary dysplasia (BPD) [34] whose O2 consumption is 25% greater [35], and functional residual capacity is 25% less [36], than in preterm infants without BPD; Equations 11 and 12 predict that such differences increase both immediate and peak SAO2 by ~70%. In addition, hypoventilation and reduced resting PAO2 in infants with BPD, as inferred from elevated PACO2 [37], further increase desaturation at apnea onset. Our finding that each rise of 1% in inspired O2 provides 1 s of delay (right-shift) in the onset of apneic desaturation (Equation 15) may guide the titration of supplemental O2 for the prevention of apneic hypoxemia while minimising the well known side-effects of long-term exposure to hyperoxia.

Our study has implications for the management of infants in clinical care. Metabolic O2 consumption can be elevated after

Figure 8. Impact of cardiac output (Qt) on SAO2. (A) Effect of three levels of resting Qt, (i) 375 ml min⁻¹ kg⁻¹, (ii) 250 ml min⁻¹ kg⁻¹, and (iii) 125 ml min⁻¹ kg⁻¹, on arterial (SAO2) and mixed venous (SVO2) O2 during apnea. Note that reduced Qt elevates SAO2, associated with a reduction in resting SVO2 and reduction in SaO2 at the stage 1–2 transition or inflection point (shown by short black lines). (B) Sensitivity of SAO2 to changes in Qt. Note the strong influence of Qt on SAnetzO2, but negligible effect on SAnetzO2 and SAnetz2O2. (C) Simulations in (A) repeated for a step change in Qt at apnea onset by (iv) +125 ml min⁻¹ kg⁻¹ (e.g. tachycardia), (v) 0 ml min⁻¹ kg⁻¹, and (vi) −125 ml min⁻¹ kg⁻¹ (e.g. bradycardia), following resting Qt=250 ml min⁻¹ kg⁻¹. Note that the transient effect of Qt is opposite to the resting effect of Qt on arterial desaturation during apnea. (D) Sensitivity of SAnetzO2 to acute changes in Qt during apnea. Note the strong influence of a step-change in Qt on SAnetzO2, but negligible effect on SAnetzO2 and SAnetz2O2. n = 'normal' values.

doi:10.1371/journal.pcbi.1000588.g008
feeding [38], with reduced ambient temperature [39], and via the administration of methylxanthines [40]. Despite the success of methylxanthines in reducing the frequency of apnea and bradycardia, such treatment has surprisingly little impact on hypoxemic episodes [41]; we suggest that the elevated O2 consumption and the absence of bradycardia are likely to increase S\textsubscript{SaO2} during those apneas that persist despite treatment. The severity of hypoxemic episodes is reduced by switching preterm infants from supine to prone [42], which may increase functional residual capacity [43] and improve diaphragm function, increase tidal volume and increase resting alveolar \textsubscript{PO2} [44]. Our finding that low cardiac output leads to increased S\textsubscript{SaO2} during apnea leads to the suggestion that judicious adjustment of inotropic support in infants with cardiac abnormalities could improve resting mixed-venous saturation and reduce apneic hypoxemia.

Hypoxemic events become less frequent between infancy and childhood, despite an unchanged apnea frequency [28], perhaps as a result of a fall in O2 consumption per body weight. However, before this occurs, infants experience a period of susceptibility to rapid desaturation during apnea as a result of a fall in hemoglobin content and O2 affinity [22] and a rise in O2 consumption [45]. The implications for SIDS are obvious in that these changes coincide with the peak incidence for SIDS at 2–3 months [46]. SIDS also occurs disproportionately in preterm infants [46], who manifest severe anemia [22] and greater O2 consumption. Infants resuscitated from apparent life threatening events have been found to have lower hemoglobin content [47], pointing to a potential role for rapid S\textsubscript{SaO2} in the progression of such events. It is possible that the rapid development of apneic hypoxemia initiates prolonged hypoxic cardiorespiratory depression that in turn leads to SIDS.

Conclusion

We have provided a mathematical framework for quantifying the relative importance of key cardiorespiratory factors on the rate of arterial O2 desaturation during apnea, with particular relevance to preterm infants. For the first time we have demonstrated that each of the factors examined has a signature influence on the trajectory of desaturation, providing quantitative insight into the causes of rapidly developing hypoxemia during apnea.
Methods

Mathematical model

**Lung compartment.** For the lung, a single homogeneous compartment is assumed based on the model of Grodins et al [48]. Each equation describing changes in the alveolar partial pressure of each gas $G$ is based on the conservation of mass (specifically, the pressure–volume product) and is expressed in terms of inspired and expired alveolar ventilation and transfer of gases into the pulmonary capillary:

$$P_{Ag} = \frac{\dot{V}_{Pb} - \dot{V}_{E} P_{Ag} - P_{0} \dot{V}_{DG}}{V_{L}}$$  \hspace{1cm} (1)

where $P_{Ag}$ represents the rate of change of alveolar $P_{O_{2}}$, $P_{CO_{2}}$, and $P_{N_{2}}$; $P_{0}$ represents the inspired alveolar partial pressure of each gas $G$; $P_{b}$ is atmospheric pressure converted from STP to BTP (863 mmHg); $\dot{V}_{DG}$ represents $\dot{V}_{Po_{2}}$ and $-\dot{V}_{PCO_{2}}$, pulmonary gas uptake (STPD) for $O_{2}$ and $CO_{2}$ ($\dot{V}_{N_{2}}$) was neglected in this study for simplicity; $V_{E}$ and $V_{I}$ are inspired and expired alveolar ventilation (BTPS). Accounting for the difference in $V_{E}$ and $V_{I}$ due to a net pulmonary gas uptake into the pulmonary blood, yields:

$$V_{E} = \frac{\dot{Q}_{b} - P_{b} - P_{Vap} V_{Total}}{P_{0}}$$  \hspace{1cm} (2)

where $\dot{Q}_{b} = \text{barometric pressure (760 mmHg)} / \dot{V}_{pap} = \text{water vapour pressure (47 mmHg)}$; $V_{Total}$ is the net pulmonary gas uptake, $V_{Total} = V_{Po_{2}} - V_{PCO_{2}}$.

Since purely obstructive apneas are relatively rare in preterm infants [49], an unobstructed airflow was chosen as the standard model in this study. In the current study it was assumed that lung volume did not fall during apnea, as in active sleep [24], when apneic desaturation events are most common [33]. With lung volume constant, conservation of mass requires that passive airflow into the unobstructed airflow must occur in response to a net pulmonary gas uptake into the pulmonary blood [11]. To account for this effect, we can write:

$$V_{I} = \frac{\dot{Q}_{b} - P_{b} - P_{Vap} V_{Total}}{P_{0}}$$  \hspace{1cm} (3)

Pilot simulations predicted that the volume of gas inflow during apnea is unlikely to exceed physiological deadspace. Thus, during apnea $P_{Ag}$ is taken as $P_{Ag}$ of the last exhaled breath prior to apnea onset.

For the current study we assumed diffusion equilibrium at the pulmonary capillaries, such that $P_{Ag} = P_{C_{G}}$. Gas uptake is determined from the Fick equation; specifically, pulmonary blood flow ($\dot{Q}_{b}$), and the difference between end capillary ($C_{G}$) and mixed venous ($C_{V_{G}}$) content:

$$\dot{V}_{DG} = \dot{Q}_{b} (C_{G} - C_{V_{G}})$$  \hspace{1cm} (4)

Utilising equations for R-L shunt, arterial content of each gas $G$ is determined from its end capillary ($C_{G}$) and mixed venous ($C_{V_{G}}$) content, and pulmonary shunt fraction ($F_{S}$):

$$C_{Ag} = (1 - F_{S})C_{G} + (F_{S})C_{V_{G}}$$  \hspace{1cm} (5)

$F_{S}$ defines the ratio of pulmonary blood flow to cardiac output, such that $F_{S} = (1 - \dot{Q}_{p}) / \dot{Q}_{t}$.

**Body compartment.** Assuming that the $P_{O_{2}}$ of the venous blood is equilibrated with the tissue $P_{O_{2}}$, the mass-balance equations are:

$$C_{V_{G}} = \frac{\dot{Q}_{T}[C_{Ag}(t-T_{A}) - C_{V_{G}}] - \dot{V}_{G}}{Q_{V_{G}}}$$  \hspace{1cm} (6)

where $C_{Ag}(t - T_{A})$ represents the gas content of $O_{2}$ and $CO_{2}$ in the arterioles; $T_{A}$ is arterial transit time; $\dot{V}_{G}$ represents $V_{O_{2}}$, and $-\dot{V}_{CO_{2}}$, the metabolic consumption of $O_{2}$ and production of $CO_{2}$; $Q_{V_{G}}$ represents $Q_{O_{2}}$, and $Q_{CO_{2}}$ the combined venous/tissue volumes for $O_{2}$ and $CO_{2}$.

Blood $O_{2}$ stores were partitioned by assigning blood volume ($Q_{b}$) to arterial (25%) and venous (75%) compartments [50] and they were modelled assuming an entirely unmixed arterial compartment, and an entirely mixed and homogenous venous compartment. The arterial transit time ($T_{A}$) is constrained by the arterial volume ($Q_{a}$) by the relationship $T_{A} = Q_{a} / \dot{Q}_{T}$. The body compartment volume $Q_{V_{O_{2}}}$ is taken as the venous volume. $Q_{CO_{2}}$, the effective venous/tissue volume for $CO_{2}$ is taken as the same value for $Q_{V_{O_{2}}}$, based on published data (see Methods – Derivation of equations). Physiologically this represents no additional contribution of a specific tissue reservoir for $CO_{2}$ within the time frame of apnea.

To characterise the $O_{2}$-dissociation curve we used a modified form of the equation of Severinghaus [51]. We re-expressed the equation with respect to the partial pressure at 50% ($P_{50}$) and at 90% ($P_{90}$) saturation:

$$S_{O_{2}} = 100[k_{2}(P_{O_{2}}^{3} + k_{1}P_{O_{2}}^{2}) + 1]^{-1}$$  \hspace{1cm} (7)

where $k_{1} = (9P_{90} - P_{50})^{3} / (P_{90} - P_{50})$ and $k_{2} = P_{50}^{-3} + k_{1}P_{50}$. Values for $P_{50}$ (24.0 mmHg) and $P_{90}$ (33.6 mmHg), were obtained from the data of Delivoria-Papadopoulos [22] for a 9-10 wk-old preterm infant. $O_{2}$ content ($C_{O_{2}}$, ml ml$^{-1}$) includes that bound to hemoglobin (Hb, g ml$^{-1}$) and that dissolved in plasma:

$$C_{O_{2}} = 1.36 Hb(S_{O_{2}} / 100) + 0.00003P_{O_{2}}$$  \hspace{1cm} (8)

The relationship between $CO_{2}$ content ($C_{CO_{2}}$) and $P_{CO_{2}}$ was assumed linear:

$$C_{CO_{2}} = \beta bCO_{2}P_{CO_{2}} + k_{CO_{2}}$$  \hspace{1cm} (9)

where $\beta bCO_{2} = 0.0048$ ml ml$^{-1}$ mmHg$^{-1}$ and $k_{CO_{2}} = 0.364$ ml ml$^{-1}$ as adapted for STPD from Grodins et al. [52].

Simulations were performed using software written in MATLAB (The Mathworks; Natick, MA).

**Theory**

**A general equation.** In an earlier study we developed a general relationship that describes the factors influencing the magnitude of $S_{O_{2}}$, at any instant in time during apnea [12]:

$$S_{O_{2}} = \frac{\beta bO_{2}P_{O_{2}}\dot{Q}_{T}}{V_{L}}(S_{O_{2}} - S_{V_{O_{2}}})$$  \hspace{1cm} (10)

where $\beta bO_{2}$ is the capacitance co-efficient of blood for $O_{2}$. To specifically demonstrate the role of gas exchange, it is more useful to represent $S_{O_{2}}$ in terms of $V_{Po_{2}}$. Using Equation 1 for $O_{2}$ under conditions of apnea ($V_{I}, V_{E} = 0$), assuming $P_{Ag} = P_{O_{2}}$, and
using $\dot{S}_{aO_2} = \beta HbO_2 P_{A O_2}$, reveals:

$$\dot{S}_{aO_2} = \frac{\beta HbO_2 P_0}{V_L} V_{PO_2}$$

(11)

where $\beta HbO_2$ (% mmHg$^{-1}$) is defined as the slope of the O$_2$-dissociation curve, specifically regarding end-capillary $P_{O_2}$ with respect to $S_{aO_2}$. It is clear from Equation 11 that $\dot{S}_{aO_2}$ is directly proportional to the product $\beta HbO_2 \times V_{PO_2}$, which both vary substantially during apneic arterial desaturation. Although Equations 10 and 11 are useful conceptually, values for $\langle S_{aO_2} - S_{vO_2} \rangle$ or $V_{PO_2}$ throughout apnea are unknown, and thus $\dot{S}_{aO_2}$ is not simple to predict explicitly.

**Special cases.** The original framework to understand factors influencing $S_{aO_2}$ was based on the assumption that $V_{PO_2} = V_{O_2}$ [10,23] which does not hold true during apnea [11,12]. However, such an assumption is valid prior to any substantial fall in $S_{aO_2}$, and as therefore useful to explicitly describe $S_{aO_2}$ immediately upon apnea onset ($S_{aO_2}^{onset}$):

$$S_{aO_2}^{onset} = \frac{\beta HbO_2 P_0}{V_L} V_{O_2}$$

(12)

Notably, Equation 12 demonstrates that for any level of $V_{O_2}$ and $V_L$, $S_{aO_2}^{onset}$ is intimately related to $\beta HbO_2$. Consequently, $S_{aO_2}^{onset}$ increases dramatically with reduced resting $P_{A O_2}$ (Figure 11).

Although no simple expression could be written to describe $S_{aO_2}$ explicitly for stage 1, we derived an expression for $S_{aO_2}$ during stage 2 (see Methods – Derivation of equations), given by:

$$\dot{S}_{aO_2}^{stage \ 2} = \frac{V_{O_2}}{1.36 \text{ Hb Qb} + \frac{V_L}{\beta HbO_2 P_0}}$$

(13)

Since the total blood O$_2$ capacity (1.36 Hb Qb) is much greater than $V_L/(\beta HbO_2 P_0)$, $S_{aO_2}^{stage \ 2}$ is determined principally by $V_L/(\beta HbO_2 P_0)$, $\dot{S}_{aO_2}^{stage \ 2}$ is determined principally by $V_L/(\beta HbO_2 P_0)$, $S_{aO_2}^{stage \ 2}$ is determined principally by $V_L/(\beta HbO_2 P_0)$, $\dot{S}_{aO_2}^{stage \ 2}$ is determined principally by $V_L/(\beta HbO_2 P_0)$, $S_{aO_2}^{stage \ 2}$ is determined principally by $V_L/(\beta HbO_2 P_0)$, $\dot{S}_{aO_2}^{stage \ 2}$ is determined principally by $V_L/(\beta HbO_2 P_0)$.

**Factors Influencing Rapid Arterial O$_2$ Desaturation**

Here we derive the explicit equations used within the current study to encapsulate key relationships pertaining to gas exchange and arterial desaturation during apnea.

**Stage 2 arterial O$_2$ desaturation.** This section details the derivation of an explicit equation to predict the rate of both arterial and venous desaturation during the severe desaturation of stage 2, a phase where $V_{PO_2}$ is substantially reduced below $V_{O_2}$, and both $S_{aO_2}$ and $S_{vO_2}$ fall at the same rate. Ignoring dissolved plasma O$_2$, consideration of Equation 1 for O$_2$ and assuming $S_{aO_2} = S_{vO_2}$ yields:

$$\dot{S}_{aO_2} = \frac{V_{O_2} - 1.36 \text{ Hb Qr}(S_{aO_2}(t-T_a) - S_{vO_2})}{1.36 \text{ Hb Qv}}$$

(15)

By substituting the following relationships into Equation 15: ($S_{aO_2}(t-T_a) - S_{vO_2}$) = $S_{aO_2}(t-T_a)$, $S_{aO_2}$ is directly proportional to the difference between $V_{O_2}$ and $V_{PO_2}$, where:

$$\dot{S}_{aO_2} = \frac{V_{O_2} - V_{PO_2}}{1.36 \text{ Hb Qb}}$$

(16)

Combining Equations 11 and 16 yields Equation 13.

**Estimation of effective blood volume for CO$_2$.** Using the same methodology as described above, the ratio of $C_{vCO_2}$ to $C_{vO_2}$, during stage 2 can be used to estimate the ratio of $Qb_{CO_2}$ to $Qb_{O_2}$, $C_{vO_2}$, and $C_{vCO_2}$ can be found using:

$$C_{vCO_2} = C_{vO_2} = -\frac{V_{G}}{Qb_{CO_2} + \frac{V_L}{\beta HbG P_0}}$$

(17)

where $Qb_{O_2}$ and $Qb_{CO_2}$ are the effective blood volumes for O$_2$/
Equation 18 permitted the calculation of $Q_{VCO2}/Q_{VO2}$ based on published data [53; their Figure 3] where during apnea the rate of rise in $C_{VCO2}$ is very close to the rate of fall in the product of $C_{VO2}$ and the respiratory exchange ratio ($RER$); using $-C_{VO2}/C_{VCO2}=1.29$ from their data, and assuming resting $RER=0.8$, we find that $Q_{bCO2}/Q_{bO2}=1.03$ or approximately 1. Thus $Q_{VCO2}/Q_{VO2}$ is assumed to be 1.

**Stage 1 hypercapnia.** Here we develop a relationship to describe the time-course of alveolar/arterial hypercapnia during stage 1 for $CO2$. Using Equation 1 for $CO2$, taking $Vl=0$, gives the relationship $P_{Aco2}=P_{vco2}/Vl$. Substituting the steady-state Fick equation, $P_{Vco2}=b_{CO2}Q_{QT}(P_{ACO2}-P_{VCO2})$, assuming alveolar-arterial equilibrium ($P_{ACO2}=P_{Aco2}$), using $P_{VCO2}=V_{CO2}$ under resting conditions, assuming that $P_{VCO2}$ is constant, and solving for $P_{Aco2}$, yields:

$$P_{Aco2}=P_{VCO2}-\frac{V_{CO2}}{b_{CO2}Q_{QT}} \exp\left(-\frac{P_{VCO2}-P_{ACO2}}{Vl}ight)$$

(19)

Calculating the rate of rise in $P_{Aco2}$ ($\Delta P_{Aco2}$) by taking the derivative gives:

$$\Delta P_{Aco2}=\frac{\Delta P_{VCO2}}{Vl} \exp\left(-\frac{P_{ACO2}}{Vl}\right)$$

(20)

Equations 19 and 20 describe the sloping of $P_{Aco2}$ from the initial rate $P_{Aco2}=P_{vCO2}/Vl$ as $P_{Aco2}$ rises towards $P_{VCO2}$. Specifically, the time constant $t=Vl/(b_{CO2}Q_{QT})$ demonstrates that high $b_{CO2}$ causes a rapid sloping of $P_{VCO2}$, and hence of $P_{Aco2}$, as the arterial value approaches venous value. Indeed, fitting an exponential curve to the $P_{Aco2}$ trace (Figure 2) during the first 5 s of apnea yielded a rapid time constant of 1.26 s, a value close to that predicted by $Vl/(b_{CO2}Q_{QT})$. The corollary is that the low value of $b_{CO2}$ prevents the sloping of $P_{VCO2}$ as desaturation progresses, giving rise to a rapid $P_{Aco2}$ decline and thus rapid arterial desaturation. Likewise, further reducing $b_{CO2}$ by lowering hemoglobin content potentiates such effect.

**Impact of supplemental $O2$.** The delay (right-shift) in arterial desaturation during apnea with increasing supplemental $O2$ ($\Delta P_{R/r}$) can be predicted explicitly. Using Equation 1 for $O2$ under the conditions of apnea, and assuming $\Delta P_{R/o}=\Delta P_{Aco2}$, the delay ($\Delta t$) in arterial desaturation is given by:

$$\Delta t=\frac{\Delta P_{R/o}Vl}{P_{0VO2}}$$

(21)

### References

1. Barrington K, Finer N (1991) The natural history of the appearance of apnea of prematurity. Pediatr Res 29: 372–375.

2. Poets CF, Stebbins VA, Samuels MP, Southall DP (1993) The relationship between bradycardia, apnea, and hypoxemia in preterm infants. Pediatr Res 34: 144–147.

3. Perlman JM, Volpe JJ (1984) Episodes of apnea and bradycardia in the preterm newborn: impact on cerebral circulation. Pediatrics 76: 333–338.

4. Janvier A, Khairy M, Kokkotis A, Cormier C, Messmer D, et al. (2004) Apnea is associated with neurodevelopmental impairment in very low birth weight infants. J Perinatol 24: 763–768.

5. Prabhukar NR, Peng YJ, Kumar GK, Pawar A (2007) Altered carotid body function by intermittent hypoxia in neonates and adults: relevance to recurrent apneas. Respir Physiol Neurobeh 157: 148–153.

6. Row BW, Kheirandish L, Neville JJ, Gozal D (2002) Impaired spatial learning and hyperactivity in rats reared in an intermittent hypoxia environment. Pediatr Res 52: 449–453.

7. Kato I, Grossasser J, Franco P, Scaillet S, Kelhmann J, et al. (2001) Developmental characteristics of apneas in infants who succumb to sudden infant death syndrome. Am J Respir Crit Care Med 164: 1464–1469.

8. Naeve RL (1974) Hypoxemia and the sudden infant death syndrome. Science 186: 837–838.

9. Poets CF, Southall DP (1991) Patterns of oxygenation during periodic breathing in preterm infants. Early Hum Dev 26: 1–12.

10. Fletcher EC, Goodnight S, Miller T, Luckett RA, Rosborough J, et al. (1990) Atelectasis affects the rate of arterial desaturation during obstructive apnea. J Appl Physiol 68: 1803–1808.

11. Lampshire EH, Rahn H (1963) Alveolar gas exchange during breath holding with air. J Appl Physiol 10: 478–482.

12. Wilkinson MH, Berger PJ, Blanch N, Broedeky V (1995) Effect of venous oxygenation on arterial desaturation rate during repetitive apneas in lambs. Respir Physiol 101: 321–331.

13. Farmer AD, Roe PG (1996) A model to describe the rate of oxyhaemoglobin desaturation during apnoea. Br J Anaesth 76: 204–291.

14. Poets CF (2004) Apparent life-threatening events and sudden infant death on a monitor. Paediatr Respir Rev 5 Suppl A: S305–306.

15. Poets CF, Rau GA, Neuber K, Gappa M, Seidenberg J (1997) Determinants of lung volume in spontaneously breathing preterm infants. Am J Respir Crit Care Med 155: 649–653.

16. Henderson-Smart DJ (1980) Vulnerability to hypoxemia in the newborn. Sleep 3: 331–342.

17. Strohl KP, Alloste MD (1984) Oxygen saturation during breath-holding and during apneas in sleep. Chest 85: 191–196.

18. Finner RN, Higgins R, Katwinkiel J, Martin RJ (2004) Prematurity mortality and the conditions of apnea. Am J Obstet Gynecol 190: 1449–1454.

19. Adams JA, Zabaleeta IA, Sackner MA (1997) Hypoxic events in spontaneously breathing premature infants: etiology basis. Pediatr Res 42: 463–471.

20. Stewart IB, Bulmer AC, Sharman JE, Ridgway L (2003) Arterial oxygen desaturation kinetics during apneic episodes in preterm infants. Arch Dis Child Fetal 66: 381–385.

21. Delovia-Papadopoulos M, Ronchovi SP, Oski FA (1973) Postnatal changes in oxygen transport of term, preterm, and sick infants: The role of red cell 2,3-Diphosphoglycerate and adult hemoglobin. Pediatric Research 5: 235–245.

22. Fletcher EC, White SG, Munafco D, Miller CC, 3rd, Luckett R, et al. (1991) Effect of cardiac output reduction on rate of desaturation in obstructive apnea. Chest 99: 452–456.

23. Stark AR, Cohan BA, Waggener TB, Frantz ID, 3rd, Kochs PC (1987) Regulation of end-expiratory lung volume during sleep in premature infants. J Appl Physiol 62: 1117–1123.

24. Cardilidge HF, Rutter N (1987) Percutaneous respiration in the newborn infant. Effect of gestation and altered ambient oxygen concentration. Biol Neonate 52: 301–306.

25. Cardilidge HF, Rutter N (1987) Percutaneous respiration in the newborn infant. Effect of ambient oxygen concentration on pulmonary oxygen uptake. Biol Neonate 54: 68–72.

26. Reink P, Asenault J, Dome V, Fortier PH, Lafond JR, et al. (2003) Active glottal closure during central apneas limits oxygen desaturation in premature lambs. J Appl Physiol 94: 1949–1954.

27. Poets CF (2003) Pathophysiology of apnea of prematurity. Implications from observational studies. In: Oommen MP, ed. Respiratory control and disorders in the newborn. New York: Marcel Dekker Inc. pp 295–316.
29. Edwards BA, Sands SA, Fenech C, Skaza EM, Brodecky V, et al. (2009) Continuous positive airway pressure reduces loop gain and resolves periodic central apneas in the lamb. Respir Physiol Neurobiol doi: 10.1016/j.resp.2009.07.006.

30. Westkamp E, Soelitt V, Adrian S, Bohahoritz B, Gronke P, et al. (2002) Blood transfusion in anemic infants with apnea of prematurity. Biol Neonate 82: 228–232.

31. Hjalmarson O, Sandberg K (2002) Abnormal lung function in healthy preterm infants. Ann J Respir Crit Care Med 165: 83–87.

32. Olhager E, Forsum E (2003) Total energy expenditure, body composition and weight gain in moderately preterm and full-term infants at term postconceptional age. Acta Paediatr 92: 1327–1334.

33. Tourneux P, Leke A, Kongolo G, Cardot V, Degrugilliers L, et al. (2008) Relationship between functional residual capacity and oxygen desaturation during short central apnic events during sleep in “late preterm” infants. Pediatr Res 64: 171–176.

34. Sekar KC, Duke JC (1991) Sleep apnea and hypoxemia in recently weaned premature infants with and without bronchopulmonary dysplasia. Pediatr Pulmonol 10: 112–116.

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

36. Hjalmarson O, Sandberg KL (2005) Lung function at term reflects severity of bronchopulmonary dysplasia. J Pediatr 146: 86–90.

37. Kaempf JW, Campbell B, Brown A, Bowers K, Gallegos R, et al. (2007) PCO2 and room air saturation values in premature infants at risk for bronchopulmonary dysplasia. J Perinatol.

38. Dechert R, Wesley J, Schafer L, LaMond S, Beck T, et al. (1985) Comparison of oxygen consumption, carbon dioxide production, and resting energy expenditure in premature and full-term infants. J Pediatr Surg 20: 792–798.

39. Hey EN (1969) The relation between environmental temperature and oxygen consumption in the new-born baby. J Physiol 199: 589–603.

40. Bauer J, Maier K, Linderkamp O, Hentschel R (2001) Effect of caffeine on respiratory control in infants with chronic lung disease. J Pediatr 130: 305–309.

41. Bucher HU, Duc G (1988) Does caffeine prevent hypoxaemic episodes in preterm babies (1000 grams or less) with chronic lung disease? Arch Dis Child Fetal Neonatal Ed 92: F347–350.

42. Wagaman MJ, Shatack JG, Moonjiani AS, Schwartz JG, Shaffer TH, et al. (1979) Improved oxygenation and lung compliance with prone positioning of neonates. J Pediatr 94: 787–791.

43. Koch G (1968) Alveolar ventilation, diffusing capacity and the A-a PO2 difference in the newborn infant. Respir Physiol 2: 228–232.

44. Wagaman MJ, Shatack JG, Moonjiani AS, Schwartz JG, Shaffer TH, et al. (1979) Improved oxygenation and lung compliance with prone positioning of neonates. J Pediatr 94: 787–791.

45. Hill JR, Rahimtulla KA (1965) Heat balance and the metabolic rate of new-born babies in relation to environmental temperature; and the effect of age and of weight on basal metabolic rate. J Physiol 190: 239–265.

46. Blair PS, Sidebotham P, Berry P, Evans M, Fleming PJ (2006) Major epidemiological changes in sudden infant death syndrome: a 20-year population-based study in the UK. Lancet 367: 314–319.

47. Poets CF, Samuels MP, Wardrop CA, Picton-Jones E, Southall DP (1992) Reduced haemoglobin levels in infants presenting with apparent life-threatening events—a retrospective investigation. Acta Paediatr 81: 319–321.

48. Grodins FS, Buell J, Bart AJ (1967) Mathematical analysis and digital simulation of the respiratory control system. J Appl Physiol 22: 260–276.

49. Milner AD, Greenough A (2004) The role of the upper airway in neonatal apnoea. Semin Neonatol 9: 213–219.

50. Guyton AC (1976) The systemic circulation. Textbook of medical physiology. 5 ed. Philadelphia: W. B. Saunders Company. pp 237–249.

51. Severinghaus JW (1979) Simple, accurate equations for human blood O2 dissociation computations. J Appl Physiol 46: 599–602.

52. Grodins FS, Gray JS, Schroeder KR, Norins AL, Jones RW (1954) Respiratory responses to CO2 inhalation; a theoretical study of a nonlinear biological regulator. J Appl Physiol 7: 283–308.

53. Hong SK, Lin YC, Lally DA, Yinn BJ, Kominami N, et al. (1971) Alveolar gas exchanges and cardiovascular functions during breath holding with air. J Appl Physiol 30: 540–547.

54. Hulskamp G, Hoo AF, Ljungberg H, Lum S, Pillow JJ, et al. (2003) Progressive decline in plethysmographic lung volumes in infants: physiology or technology? Am J Respir Crit Care Med 168: 1003–1009.

55. Hill JR, Robinson DC (1968) Oxygen consumption in normally grown, small-for-dates and large-for-dates new-born infants. J Physiol 199: 685–703.

56. Walther FJ, Siassi B, Ramadan NA, Ananda AK, Wu PY (1985) Pulsed Doppler response to CO2 inhalation; a theoretical study of a nonlinear biological regulator. J Appl Physiol 7: 283–308.

57. multicentre study of the respiratory control system. J Appl Physiol 22: 260–276.

58. Koch G (1968) Alveolar ventilation, diffusing capacity and the A-a PO2 difference in the newborn infant. Respir Physiol 2: 228–232.

59. Koch G (1968) Alveolar ventilation, diffusing capacity and the A-a PO2 difference in the newborn infant. Respir Physiol 2: 228–232.

60. Koch G (1968) Alveolar ventilation, diffusing capacity and the A-a PO2 difference in the newborn infant. Respir Physiol 2: 228–232.
Author/s: Sands, SA; Edwards, BA; Kelly, VJ; Davidson, MR; Wilkinson, MH; Berger, PJ

Title: A Model Analysis of Arterial Oxygen Desaturation during Apnea in Preterm Infants

Date: 2009-12-01

Citation: Sands, S. A., Edwards, B. A., Kelly, V. J., Davidson, M. R., Wilkinson, M. H. & Berger, P. J. (2009). A Model Analysis of Arterial Oxygen Desaturation during Apnea in Preterm Infants. PLOS COMPUTATIONAL BIOLOGY, 5 (12), https://doi.org/10.1371/journal.pcbi.1000588.

Persistent Link: http://hdl.handle.net/11343/242867

File Description: published version

License: CC BY