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Unstable SpO_2 in preterm infants: The key role of reduced ventilation to perfusion ratio

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Introduction: Instability of peripheral oxyhemoglobin saturation (SpO_2) in preterm infants is correlated with late disability and is poorly understood. We hypothesised that a reduced ventilation to perfusion ratio (V_A/Q) is the key predisposing factor for SpO_2 instability.

Methods: We first used a mathematical model to compare the effects of reduced V_A/Q or shunt on SaO_2 stability (SaO_2 and SpO_2 are used for model and clinical studies respectively). Stability was inferred from the slope of the SaO_2 vs. inspired oxygen pressure (P_IO_2) curve as it intersects the 21 kPa P_IO_2 line (breathing air). Then, in a tertiary neonatal intensive care unit, paired hourly readings of SpO_2 and P_IO_2 were recorded over a 24 h period in week old extremely preterm infants. We noted SpO_2 variability and used an algorithm to derive V_A/Q and shunt from the paired SpO_2 and P_IO_2 measurements.

Results: Our model predicted that when $V_A/Q < 0.4$, a 1% change in P_IO_2 results in >8% fluctuation in SaO_2 at 21 kPa P_IO_2. In contrast, when a 20% intrapulmonary shunt was included in the model, a 1% change in P_IO_2 results in <1% fluctuation in the SaO_2. Moreover, further reducing the V_A/Q from 0.4 to 0.3 at 21 kPa P_IO_2 resulted in a 24% fall in SaO_2. All 31 preterm infants [mean gestation (±standard deviation) 26.2 (±1) week] had $V_A/Q < 0.74$ (normal >0.85) but only two infants had increased shunt at 1.1 (±0.5) weeks' postnatal age. Median (IQR) SpO_2 fluctuation was 8 (7)%. The greatest SpO_2 fluctuations were seen in infants with $V_A/Q < 0.52$ (n = 10): SpO_2 fluctuations ranged from 11%–17% at a constant P_IO_2 when $V_A/Q < 0.52$. Two infants had reduced V_A/Q and increased shunt (21% and 27%) which resolved into low V_A/Q after 3–6 h.

Discussion: Routine monitoring of P_IO_2 and SpO_2 can be used to derive a hitherto elusive measure of V_A/Q. Predisposition to SpO_2 instability results from reduced V_A/Q rather than increased intrapulmonary shunt in preterm infants with cardiorespiratory disease. SpO_2 instability can be prevented by a small increase in P_IO_2.

KEYWORDS

infant, premature, neonatal intensive care unit, pulmonary gas exchange, oxygen inhalation therapy

1 Introduction

Peripheral oxyhemoglobin saturation (SpO_2) instability may result in more than 100 hypoxemic events per day within the first 8 weeks of life in preterm infants (Di Fiore et al., 2010). Moreover, SpO_2 instability is poorly documented despite the correlation with an increased rate of late death or disability at 18 months of age (Poets et al., 2015). SpO_2 instability increases when the infant is in supine compared to the prone position, independent of the mode of respiratory support (Miller-Barmak et al., 2020). A contributing factor for hypoxemic episodes in preterm infants includes sudden decrease in lung volume leading to small airway collapse and intrapulmonary shunt (Bolivar et al., 1995). We have previously shown in adults that SpO_2 was unstable when ventilation to perfusion ratio (V_A/Q) was reduced, but was stable with increased shunt (Jones and Jones, 2000).

The concept of V_A/Q is well established but infrequently used in neonatal practice, as the technics for measuring V_A/Q in infants are technically difficult e.g. A-a nitrogen difference, or impossible e.g. Multiple Inert Gas Elimination Technique (MIGET) (Corbet et al., 1974; Hand et al., 1990; Roca and Wagner, 1994). Our non-invasive method for measuring V_A/Q in adults is based on the different effects on SpO_2 of changing inspired oxygen pressure (P_IO_2) when either V_A/Q is reduced or shunt increased (Jones and Jones, 2000). The method depends on the shape of the oxyhaemoglobin dissociation curve (ODC). We adapted this method for preterm infants by using the neonatal rather than the adult ODC as the reference and plotting SpO_2 at different P_IO_2 (Lockwood et al., 2014). A computer algorithm derived a model of V_A/Q and shunt from the paired SpO_2 and P_IO_2 dataset. Decreasing V_A/Q is reflected by a right shift of the SpO_2 vs. P_IO_2 curve. The right shift leads to a steeper slope of the curve as it intersects the 21 kPa P_IO_2 line (P_IO_2 = F_IO_2 x (barometric pressure—saturated water vapour pressure), which means 21 kPa P_IO_2 is equal to room air at sea level (Figure 1). Any paired SpO_2 vs. P_IO_2 measurement located on the steep section of the ODC may predispose the infant to SpO_2 instability with small changes in alveolar oxygen.

We hypothesised that SpO_2 instability in preterm infants with cardiorespiratory disease is not an epiphenomenon but an important clinical sign of a reduced V_A/Q rather than right to left intrapulmonary shunt. We used a new algorithm and routine SpO_2 monitoring to derive V_A/Q and shunt.

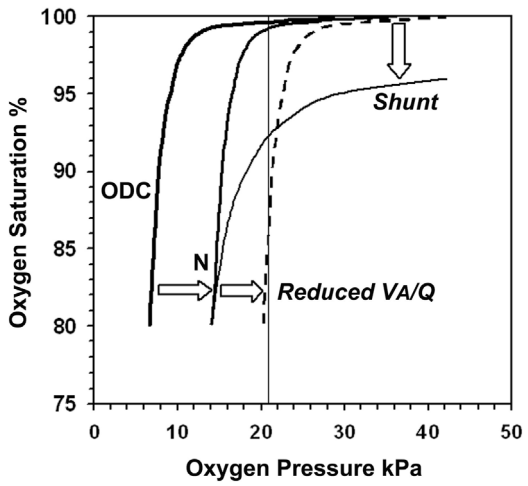

FIGURE 1
The neonatal oxyhaemoglobin dissociation curve is derived by plotting oxygen saturation (SaO_2) against arterial oxygen pressure (PaO_2) and determines the shape of the normal infant SpO_2 vs. P_IO_2 curve (N), which is displaced to the right proportional to PCO_2. Reducing Ventilation to Perfusion ratio (V_A/Q) shifts the curve further to the right (dashed line). Its slope is now steep as it intersects the 21 kPa P_IO_2 line where a 1% change in P_IO_2 results in large SpO_2 instability. Shunt displaces the plateau downwards with trivial effect on stability.

2 Methods

We conducted a prospective observational study in two phases. Firstly, we used a mathematical model of pulmonary gas exchange to examine changes in V_A/Q or increasing shunt on the slope of the SpO_2 vs. P_IO_2 curve.

Secondly, we recorded 24 hourly SpO_2 vs. P_IO_2 measurements in extremely preterm infants requiring continuous SpO_2 monitoring. From these measurements, we derived V_A/Q and shunt using a pulmonary gas exchange algorithm (Lockwood et al., 2014).

2.1 Gas exchange model

We explored the effects of reducing V_A/Q or increasing shunt on the arterial oxygen saturation (SaO_2) vs. P_IO_2 curve using a mathematical model of pulmonary gas exchange described by Olszowka and Wagner (Olszowka et al., 1980). Datasets were generated using the equations implemented on a spreadsheet supplied by Dr AJ Olszowka. The model allowed calculation of exact values of SaO_2 for a given P_IO_2. The model lung is subdivided into three compartments: a shunt and two ventilated regions with different alveolar ventilation-perfusion ratios (V_A/Q). The values of cardiac output, oxygen consumption, hemoglobin concentration, shunt fraction, and the distribution of blood flow and alveolar ventilation to the ventilated compartments can be set. The perfusion of one compartment was set at 90% of non-shunt flow while V_A/Q was reduced stepwise from 0.85 to 0.3. Shunt was fixed at 2%, P_IO_2 was varied between 15 kPa and 30 kPa (F_IO_2 = 0.15–0.3) and the SaO_2 was derived at the corresponding P_IO_2. In the next step, the V_A/Q was kept constant at 0.85 and the shunt was increased stepwise from 2%–25%. The P_IO_2 was again varied between 15 and 30 kPa (F_IO_2 = 0.15–0.3) and the corresponding SpO_2 recorded. The slope of the SpO_2 vs. P_IO_2 curve was calculated as it intersected the 21 kPa P_IO_2 line (F_IO_2 = 0.21).

2.2 Clinical study

2.2.1 Study design

We conducted a prospective observational study at King Edward Memorial Hospital in Perth in Western Australia. The study was approved by the Women and Newborn Health Service Human Research Ethics Committee (HREC:1883EW and 20130193EW) in Perth.

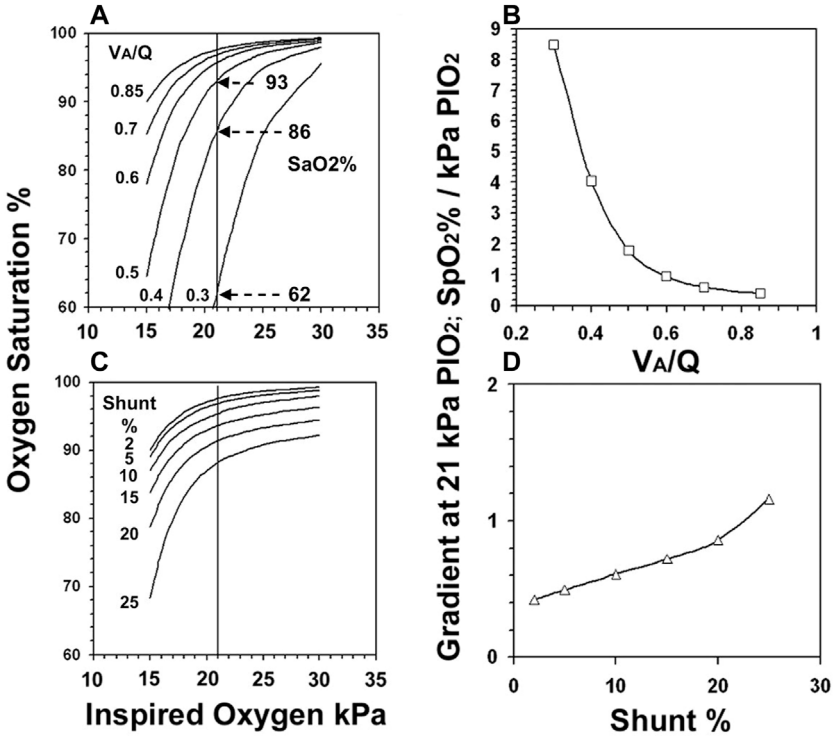

FIGURE 2
The gas exchange model derived P_IO_2 vs. SaO_2 curves when V_A/Q was reduced from 0.85 to 0.3. (Figure 2A). The slope of the curve as it intercepted the 21 kPa P_IO_2 line is shown for V_A/Q (Figure 2B). The P_IO_2 vs. SaO_2 curves when shunt increased from 2%–25% (Figure 2C) and their slopes (Figure 2D).

2.2.2 Recruitment period, inclusion and exclusion criteria

Preterm infants born ≤28 weeks' gestation without major congenital malformations were recruited from the Neonatal Clinical Care Unit at King Edward Memorial Hospital for Women in Perth, Western Australia (KEMH) between 21st August 2017 and the 1st February 2018. All included infants were part of the Preterm Infant Functional and Clinical Outcomes (PIFCO) study (ACTRN12613001062718). We started recruitment for this substudy based on the findings from the main PIFCO cohort, hence the shorter recruitment period and the much smaller number of infants included in the study (Svedenkrans et al., 2019). Informed consent was obtained from parents before the first measurement.

2.2.3 Conduct of study

Infants were assessed at 1 week of age. SpO_2 measurements were recorded at hourly intervals for 24 h (Masimo Infant Pulse Oximeter Adhesive Sensor RD SET® Inf; Philips Monitor. IntelliVue MP50 or MP70 Neonatal). Measurements were postponed until the following day in infants with changing respiratory support on the day of measurement. F_IO_2 was adjusted by the bedside nurses to achieve a SpO_2 within the target range SpO_2 90%–94%. F_IO_2 was later converted into P_IO_2 (P_IO_2 = F_IO_2 x (barometric pressure – saturated water vapour pressure).

2.2.4 Analysis of results

The slope of the SpO_2 vs. P_IO_2 curve in preterm infants was analysed using the pulmonary gas exchange algorithm with three lung compartments (Lockwood et al., 2014). Reference normative data of V_A/Q, right shift of the oxyhemoglobin dissociation curve and right to left shunt in healthy term infants studied in the first week of life were used to quantify the magnitude of the abnormalities in our population of extremely preterm infants (Dassios et al., 2017; Dassios et al., 2019).

2.2.5 Background data

Patient data information including duration of respiratory support and oxygen therapy were collected from the medical charts or the discharge summaries.

2.2.6 Statistical analyses

Study data were collected and managed using Research Electronic Data Capture (REDCap) software hosted at The

TABLE 1 Demographics of infants studied (*n* = 31).

Male (n, %)	20 (64.5)
GA (w)	26.2 ± 1.0
Age at Test (w)	1.1 (0.5)
Weight at birth (g)	890 ± 196
Mechanical Ventilation at test (n, %)	8 (26.0)
Non-invasive respiratory support at test (n, %)	23 (74.0)

GA, gestational age; w, week; g, gram. Values are reported as mean ± SD, median (IQR) or n (%).

University of Western Australia. REDCap is a secure, web-based application designed to support data capture for research studies (Harris et al., 2009).

Parametric data are reported as mean and standard deviation (SD) and non-parametric data as median and variance. Statistical analyses included Student's *t*-test for the comparison of parametric and Mann-Whitney-U test for the comparison of non-parametric data. Data were analysed within SPSS (v25·0·0·1; IBM Corp, United States).

3 Results

3.1 Gas exchange model

Reducing V_A/Q shifted the SaO_2 vs. P_IO_2 curve to the right so that its slope increased as it intercepted the 21 kPa P_IO_2 line (Figure 2A). SaO_2 at the intercept fell in increasingly large increments particularly with V_A/Q below 0.5: e.g., a 24% SaO_2 fall when V_A/Q dropped from 0.4 to 0.3. The effect of V_A/Q on the slope of the curve (Figure 2B)

TABLE 2 Measurements of included infants.

Infant number	MV	V_A/Q	Shift kPa	P_IO_2kPa	Number of SpO_2 at that P_IO_2	Min SpO_2%	Med SpO_2%	Range SpO_2%	Variance SpO_2%
1	N	0.52	11.6	21	24	93	98	14	6.8
2	N	0.49	12.4	22	15	83	94	15	11.0
3	Y	0.22	27.5	35	14	90	94	8	6.0
4	N	0.21	28.8	38	5	88	95	9	28.8
5	N	0.27	22.8	30	14	87	93	9	5.9
6	Y	0.31	19.2	27	13	84	96	13	16.9
7	N	0.5	12.0	21	24	93	97	6	3.3
8	N	0.73	8.3	21	24	96	98	4	1.5
9	Y	0.46	13.3	21	19	91	95	6	3.3
10	N	0.56	10.8	21	24	97	98	3	0.6
11	N	0.57	10.6	21	24	96	99	4	1.7
12	N	0.54	11.3	21	24	96	98	4	1.6
13	Y	0.35	17.5	25	15	91	94	5	2.1
14	N	0.3	20.0	28	17	90	96	8	4.0
15	N	0.39	15.4	24	8	84	91	14	22.3
16	N	0.49	12.3	21	24	93	96	7	2.8
17	N	0.3	20.2	28	16	91	95	5	2.7
18	N	0.49	12.4	21	19	92	96	7	4.1
19	Y	0.24	25.0	32	10	84	93	14	17.5
20	Y	0.27	22.6	30	12	88	94	8	7.7
21	N	0.28	22.7	30	12	88	93.5	9	8.4
22	Y	0.3	20.1	30	9	89	95	8	6.3
23	N	0.44	13.8	21	14	81	93	16	16.8
24	N	0.27	22.8	30	10	81	94	17	22
25	N	0.47	12.8	21	24	91	95	8	3.7
26	N	0.52	11.6	21	24	95	97.5	4	11.6
27	N	0.35	17.3	25	13	92	94	6	17.3
28	N	0.39	15.5	23	10	86	94	12	15.5
29	N	0.47	12.8	21	24	92	96	5	12.6
30	N	0.27	22.8	30	13	84	93	12	22.8
31	Y	0.29	20.8	28	9	87	94	11	20.8

Spot reading of SpO_2 and P_IO_2 at 1 h intervals within a 24 h monitoring period. Infant 3 had four readings at P_IO_2 78, 92, 92 & 91 kPa from 3–6 h to derive a 27% shunt, V_A/Q 0.24 and shift of 34.1 kPa. From 10–24 h the 27% shunt resolved at constant 35 kPa P_IO_2 to a single compartment V_A/Q of 0.22 and 27.4 kPa shift. MV, mechanical ventilation.

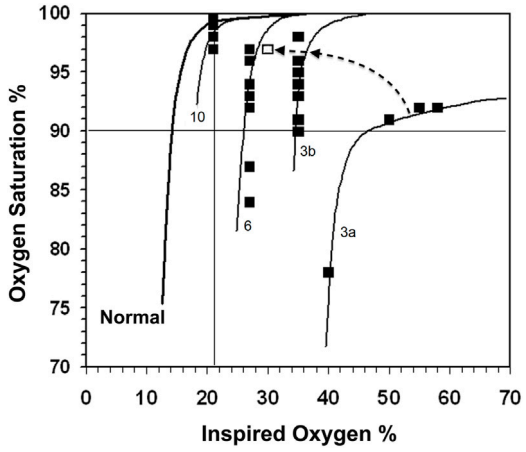

FIGURE 3
The normal P_IO_2 vs. SpO_2 curve is shown on the left. SpO_2 readings (closed boxes) with the calculated gas exchange model curves for infants 3, 6 and 10. Infant 3 had 27% shunt and V_A/Q of 0.24 (3a), which resolved during the day to a single V_A/Q compartment of 0.22 and a SpO_2 range of 8% (3b) and subsequently into a final point (open box) at the end of the day to almost overlying the V_A/Q 0.31 line of infant 6 (the changes are indicated by the dashed arrow). Infant 6 initially had a 21% shunt and V_A/Q of 0.43 (not shown in Figure), which resolved into a V_A/Q of 0.31 in the 9–24 h study period. Infant 10 had a V_A/Q of 0.56 and a SpO_2 range of 3% from 24 SpO_2 values.

suggested an unstable SaO_2 once V_A/Q fell below 0.5: a 1% change in P_IO_2 at 0.3 V_A/Q resulted in a >8% change in SaO_2.

In contrast, increasing shunt (Figure 2C) displaced the curve downwards but even large changes in P_IO_2 caused only small changes in both SaO_2 and slope (Figure 2D): for example in the setting of a 20% intrapulmonary shunt, a 1% change in P_IO_2 resulted in <1% change in SaO_2.

3.2 Clinical study

We studied 31 extremely preterm infants (mean (SD) 26.2 (1.0) weeks' gestation) at median (IQR) 1.1 (0.5) weeks' postnatal age. Eight infants were mechanically ventilated and 23 infants were on non-invasive respiratory support during the measurements. Demographics for this infant cohort are shown in Table 1.

Ten infants received 21 kPa P_IO_2 throughout the 24 h monitoring period. Median (IQR) P_IO_2 in the remainder was 28 (Jones and Jones, 2000) % to maintain target SpO_2 90%–94%. The number of consecutive hourly readings at the same P_IO_2 in each infant are shown in Table 2. There were sufficient data to describe the steep part of the SpO_2 vs. P_IO_2 curve in all infants in terms of V_A/Q and shift, but complete characterization of the top end of the curve was constrained by the upper limit of the SpO_2 target range and therefore restricted P_IO_2. The V_A/Q was less than 0.74 in every infant and only two infants (Nr. 3 and 6) had a large shunt resolving after a few hours into predominantly low V_A/Q compartments. The median (IQR) SpO_2 of all preterm infants was 8.0 (7.0) % at a constant P_IO_2 over at least 5 h. At a $V_A/Q < 0.52$, in 10 out of 31 infants the variability of the SpO_2 ranged from 11%–17%, whereas in the four infants with $V_A/Q > 0.52$, the range of SpO_2 recorded was ≤4% (V_A/Q 0.73, 0.56, 0.57, 0.54). Seven infants had a profound desaturation with a $SpO_2 \leq 84\%$. All seven infants had a $V_A/Q \leq 0.49$ and four of them $V_A/Q < 0.31$. Examples of the pattern of SpO_2 in three infants are shown in Figure 3 using the gas exchange algorithm (Lockwood et al., 2014) and a format similar to Figure 1.

One infant (Nr. 3) required a $P_IO_2 > 50$ kPa to maintain SpO_2 within the target range. This infant had an initial large shunt and greatly reduced V_A/Q, which later resolved into a single low V_A/Q compartment. Infant Nr. 3, 6 and 10 are described in detail in the legend to Figure 3.

The 10 infants exhibiting the most variable SpO_2 (range >10% in SpO_2) were equally distributed between those breathing spontaneously (n = 5) and those requiring mechanical ventilation

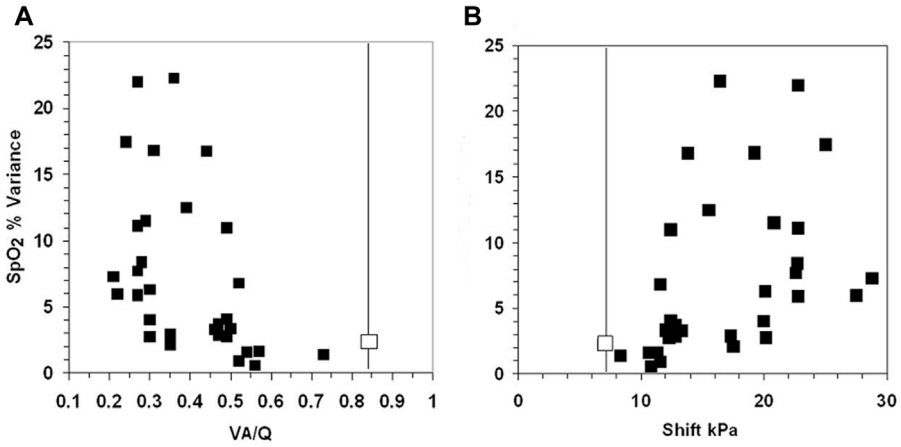

FIGURE 4
The fall in V_A/Q below 0.52 (Figure 4A) and an increase in shift >11 kPa (Figure 4B), were associated with an abrupt widening of the variance of SpO_2. The two uppermost points have a range of 16% and 17% SpO_2 in infants 23 and 24. The normal values for V_A/Q and shift are shown by the vertical line. The normal variance for SpO_2 is 2.2 shown by the contrasting boxes on the vertical line (Dassios et al., 2017; Dassios et al., 2019).

(n = 5) (Table 1). The increased variance in SpO_2 as V_A/Q falls below 0.5 is illustrated in Figure 4A shift increases >11 kPa in Figure 4B.

4 Discussion

We suggest that a reduced V_A/Q predisposes preterm infants to SpO_2 instability. The pulmonary gas exchange model showed that reducing V_A/Q shifted the P_IO_2 vs. SaO_2 curve to the right, whereas shunt displaced the curve downwards. Right shift increased the effective curve slope up to 16 times where it intercepted the 21 kPa P_IO_2 line e.g., breathing room air. The right shift predicted large fluctuations in SaO_2 with small changes in alveolar oxygen. Reducing V_A/Q from 0.4 to 0.3 predicted a 24% fall in SaO_2 breathing air. In contrast a large shunt had little effect on curve slope and a small fall in SaO_2.

These predictions were confirmed in extremely preterm infants by routine monitoring of SpO_2 and P_IO_2. The paired SpO_2 vs. P_IO_2 measurements were used to derive V_A/Q, right shift and shunt using Lockwood's algorithm (Lockwood et al., 2014). All infants had a reduced V_A/Q. The SpO_2 was unstable with a median (IQR) 8.0 (7.0) % at a constant P_IO_2 compared to a mean (±SD) of 3% (±1.5%) in healthy newborn infants breathing room air (Dassios et al., 2017; Dassios et al., 2019). Infants with $V_A/Q < 0.52$ had considerable increase in SpO_2 variability, seven infants had episodes with $SpO_2 \leq 84\%$, whilst four of these infants were dependent on supplemental oxygen ≥27%. Two infants had transient shunt lasting for a few hours, which was not associated with SpO_2 instability. In the remaining infants, the P_IO_2 was insufficiently high to fully characterize shunt due to the SpO_2 target range (90%–94%).

The non-invasive method for deriving V_A/Q and shunt normally depends on varying P_IO_2 (Rowe et al., 2010; Bamat et al., 2015; Dassios et al., 2017; Dassios et al., 2019; Svedenkrans et al., 2019; Bamat et al., 2022). More recently, we showed that V_A/Q and/or shift can be derived from serial SpO_2 measurements at a fixed P_IO_2 (Svedenkrans et al., 2019; Stoecklin et al., 2021). A reduced V_A/Q lowers SpO_2 at any given P_IO_2 and increases the effective slope of the SpO_2 vs. P_IO_2 curve, but does not by itself make SpO_2 unstable unless V_A/Q itself is unstable (Jones, 2021). The reduced V_A/Q amplifies the destabilizing effects on SpO_2 during changes in cardiac output, ventilation, central or obstructive apnea and posture. Interestingly, the 10 infants with the most unstable SpO_2 were equally distributed between those breathing spontaneously and those on mechanical ventilation. Reduced V_A/Q can lead to SpO_2 instability independent of the mode of respiratory support used in an infant.

In agreement with our results, a reduced V_A/Q in adults leads to SpO_2 instability breathing room air. By adding a time dimension, the different effects of V_A/Q or shunt in individual adult patients breathing air is more clearly illustrated by dynamic waterfall plots of continuously monitored SpO_2 (Entwistle et al., 1991; Jones and Jones, 2000; Jones, 2021) than do "static" histograms (Borenstein-Levin et al., 2020). A typical example of unstable SpO2 in a patient with reduced V_A/Q breathing air is shown in Figure 3 in Ref (Jones, 2021). This patient had blunt curves with SpO_2 fluctuating from 77% to 95%. In contrast, a patient with increased shunt had superimposed stable SpO_2 peaks within a much narrower SpO_2 range.

We note that the right to left shunt in our study might include some element of cardiac shunting occurring *via* an open ductus arteriosus. Our method does not allow differentiation between intrapulmonary or cardiac shunt. However, in the majority of preterm infants the ductus arteriosus would have functionally closed on day seven of life. In the few infants with a persistent ductus arteriosus, at day seven of life a predominantly left to right shunt would be expected which would not affect our calculations (de Klerk et al., 2020).

The clinical applicability of our findings is that routine measurements of SpO_2 and P_IO_2 can be analysed with our algorithm to derive V_A/Q and shunt, thereby characterizing respiratory disease in preterm infants. V_A/Q and shunt incorporate information on the mechanisms of hypoxemia and explain SpO_2 instability. Consequently, SpO2 instability can be prevented by a small increase in P_IO_2.

5 Conclusion

In conclusion, we reported that predisposition to oxygen saturation instability in preterm infants results from a reduced ventilation to perfusion ratio rather than from increased intrapulmonary shunt. We have highlighted how routine monitoring can be used to derive non-invasive measurements of oxygenation impairment in preterm infants. Future research should aim at strategies to not only detect SpO_2 instability, but to also prevent such instability.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was approved by the Women and Newborn Health Service Human Research Ethics Committee (HREC:1883EW and 20130193EW) in Perth. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

BS collected and analysed the data, interpreted the data, assisted with the REDCap database design and development, drafted the initial manuscript together with JGJ, performed literature search, and approved the final manuscript as submitted. YC collected the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. JGJ developed the algorithms used for the calculation of shunt, shift and VA/Q, drafted reviewed and revised the manuscript, drafted the Figures and approved the final manuscript as submitted. GL developed the algorithms used for the calculation of shunt, shift and VA/Q, reviewed and revised the manuscript. TD drafted the initial manuscript, revised and approved the final manuscript. JP was the principal investigator obtaining funding, leading study design including development of the REDCap database, verified all statistical calculations, interpreted the data, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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