COMPARISON OF THE RELATIVE CHANGE IN THE RATIO OF PaO_2 AND FiO_2 DURING PERIODS OF CONTROLLED THERAPEUTIC INTERVENTION AND ROUTINE CARE

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Abstract

Oxygen is the most common drug used in the critical care of infants. There is significant morbidity and mortality associated with excess or inadequate levels. For this reason, an important element of many therapeutic interventions in the ICU requires assessment of their acute impact on oxygenation. It is common to normalize the arterial level of oxygen with the fraction of inspired oxygen (PF-ratio). Further, a change may often be more important than the absolute level. Though the PF-ratio is often reported, it was surmised that the rarely reported, relative magnitude of change in PF-ratio might be a useful metric for assessing the stability and effectiveness of therapy. Therefore, individual patient data from two different studies were evaluated. The cases included periods of therapeutic intervention and periods without intervention, thus permitting the evaluation of the PF-ratio's potential sensitivity to change and thresholds for relevant change. During surfactant administration in extremely preterm infants, the PF-ratio improved at least 25% in 91% of the infants, while 9% showed less than a 10% change. During high-frequency oscillatory rescue in children, the PF-ratio improved at least 25% in 76% of the infants, while 8% showed less than a 10% change. Consideration of thresholds of 50% and 5% reflected low prevalence. In periods of routine care, the prevalence of marked changes was less prevalent but still common (6% and 55%) and periods of little change more prevalent (21% and 21%). We believe this initial work supports the feasibility of using the magnitude of change in PF-ratio and provides a useful stimulus for additional evaluations.

Keywords

neonatal and pediatric critical care, oxygenation

Background

Oxygen is the most common drug administered in the critical care of infants. There is significant morbidity and mortality associated with excess or inadequate oxygenation. For this reason, an important element of many therapeutic interventions in the ICU requires assessment of their impact on oxygenation. Oxygenation is commonly monitored with a noninvasive oximeter, but the gold standard is a periodic assessment of arterial oxygen tension (PaO_2).

It is common to normalize the arterial level of oxygen by dividing it by the fraction of inspired oxygen (PF-ratio). This is important because the therapeutic goal is to maintain arterial oxygenation in a narrow range by titrating inspired oxygen (FiO_2) up or down. In routine clinical practice changes, oxygenation is often reported as a change in FiO_2. However, the corresponding acceptable level of arterial oxygen is a range, not a value (e.g., 50–80 mmHg). This wide range results in reported FiO_2 changes being imprecise and potentially misleading. For this reason, the PF-ratio is much preferred and an essential, accepted element of defining the severity of respiratory distress [1]. Further, the occurrence of a relevant change, up or down, may often be more important than the absolute level. Though the PF-ratio is often reported, the rarely reported magnitude of the change in PF-ratio might be a helpful metric for assessing the effectiveness of therapy. Furthermore, it might be useful for communicating changes in individual patients and assessing response to a controlled therapeutic intervention in clinical research.

A decision was made to explore this by evaluating individual subject data from clinical studies with respiratory interventions.

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Methods

This study was conducted to explore the potential of using the percent change in PF-ratio as a metric for evaluating clinically relevant change in an environment of normal clinical variation. The intent was to evaluate individual patient data from clinical studies with distinct periods of therapeutic intervention and routine clinical variation. The supposition was that there is potential for this normalized metric to measure an individual patient's response and group response in clinical research evaluations.

Our repository was reviewed to look for studies in infants and children that meet several criteria: 1) clear periods of therapeutic intervention and routine care, 2) availability of individual subject data and 3) protocolized PF-ratio measurements. Two studies were identified that met these criteria. The first study evaluated the response to administration of surfactant in 67 extremely preterm newborns [2]. PF-ratio data were available at baseline, 12, 24, and 48 hours. The second was a multicenter experience describing 303 infants and children receiving rescue high-frequency oscillatory ventilation (HFOV) intervention in the pediatric ICU [3]. PF-ratio data were available at baseline 3, 6, 12, 24, 48, and 72 hours. Based on this availability and experience with these populations, the intervention period was defined as the first 24 hours and routine care as 24–48 and 48–72 hours. All these paired periods were not available for all the subjects.

Four categorical endpoints were selected for evaluation, based on a judgment from experience with many similar studies. For a significant change, 25% and 50% or greater were selected. Thresholds of less than 10% and 5% were selected as lacking clinical relevance change and thus reflective of normal within-day clinical variation. The absolute value of percent change in PF-ratio was used. We thus included the direction of change as a secondary parameter.

This was an initial exploratory study without hypotheses. Confidence limits (95%) of the proportion or mean, as appropriate, were calculated with an inference of statistical difference if they did not overlap. All data were analyzed using Excel (v16.42, Microsoft USA).

Results

We analyzed data from two studies. The data from the first study reflected the response to the administration of surfactant in 61 preterm newborns (median gestational age 27 weeks (IQR 25–28) in the first two days of life in the ICU. The second data set was a multicenter experience including 237 children (median age nine months, IRQ 1–48 months) receiving rescue HFOV intervention in the ICU.

Figure 1 shows the response for each intervention in the first 24 hours (protocolized PF-ratio measurements). It presents the mean value with a confidence interval for the pooled infants. There was a clear response within 12 hours to surfactant administration. The initial PF-ratio of 135 reached 236 at 24 hours, an average increase of 75%. Although not shown in this chart, the PF-ratio had plateaued and was similar at 48 hours (196, IQR 163–230). As would be expected, the PF-ratio of the HFOV rescue group was initially much lower (109) but also showed significant improvement at 3, 6, and 12 hours and reached 161 by 24 hours. The average increase was 48% in 24 hours. The PF-ratio associated with HFOV had plateaued and was similar at 48 (169, IQR 162–177) and 72 hours (166, IQR 157–174). In both studies, the magnitude confidence intervals of the mean suggests that the response was varied among subjects but still represents a statistically significant improvement for the group during the 24 hour intervention period.

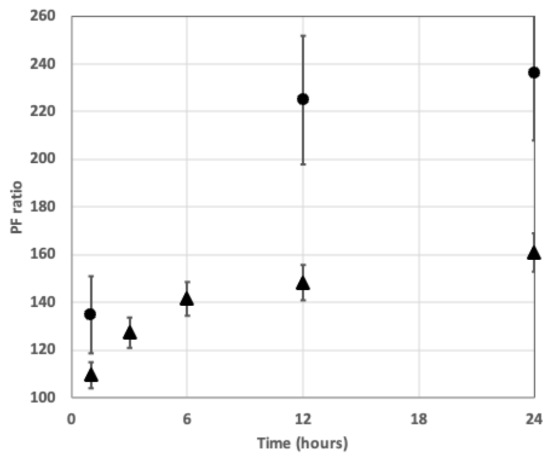

Fig. 1: PF-ratio Change with Intervention. Circles reflect surfactant administration and triangles HFOV. Whiskers show the 95% confidence limits of the mean.

The results of our primary metrics, response are shown in Table 1. The table details the breakdown by study group, plus a cross-tabulation by the two periods (intervention and routine). Marked changes (25% and 50%) were lower but prevalent during the periods of intervention. They also varied depending on the threshold and the intervention. The response to surfactant administration was larger (91% increased 25% or more and 76% increased 50% or more). In comparison, the response to HFOV intervention was 76%, with an increase of 25% or more, and 57% increased 50% or more. The differences between the two groups' changes and each between the thresholds were all statistically significant.

Correspondingly limited changes (less than 10% and 5%) were much less prevalent during the intervention period, specifically all less than 10%.

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Table 1: Primary Response Metrics. The intervention period (noted as I) and the non-intervention period (noted as NI). The 95% confidence limits of the prevalence (proportion) are shown as (lower–upper).

Study	Surf	Surf	HFOV	HFOV
Period	I	NI	I	NI
number	61	46	149	237
5%	2 (1–2)	10 (9–12)	0.5 (0.4–0.6)	11 (10–12)
10%	9 (8–10)	21 (19–22)	8 (7–9)	21 (19–23)
25%	91 (90–92)	67 (65–69)	76 (74–79)	55 (52–58)
50%	76 (70–82)	38 (36–41)	57 (53–60)	26 (23–28)

Surprisingly, 25% and 50% marked changes were also prevalent during the routine period, but was statistically less than during the intervention period. These large changes were slightly more prevalent in the surfactant group than in the HFOV group (25% change: 67% vs. 55%, and 50% change 38% vs. 26%). In contrast, the prevalence of small changes did not vary significantly among the thresholds and the intervention type (10% change: 20% vs. 11%, and 5% change: 21% vs. 21%).

The relationship between the direction of change and the size of the change was also examined. Small changes were equally likely to increase as to decrease (48%/53% respectively), while larger changes were four times as likely to increases (74%/26% respectively). These were not different between the intervention period and the routine period.

Discussion

We evaluated nearly 500 daily changes in PF-ratio in almost 300 infants. About a quarter of these were during the investigational therapeutic intervention and the balance during routine ICU care following the intervention. This work aimed to evaluate the percent change in PF-ratio as a metric. The pooled data showed that the group improved during the experimental interventions and was stable following it. However, the response categorization illustrated that there were many infants with marked changes in PF-ratio during periods of stability and that a relevant number of infants did not have any relevant change in periods of intervention. Thus considering PF-ratio change did add detail beyond just considering the population's pooled response or lack thereof.

Two sets of thresholds were evaluated in two different populations, each with experimental intervention and routine care. Large changes were markedly different between preterm infants with respiratory failure and severe pediatric respiratory distress. This was true during the active intervention period and the routine care period. This suggests that when determining if there is a relevant improvement, either with a change in therapy or during routine care, the threshold level might be optimized by considering both the specific intervention and the patient population. It is unclear if the differences reported are due to the patient population's severity or the type of intervention. One can speculate that it is to some degree both.

In contrast, the magnitude of small changes was not markedly different when considering the patient population. Thus, one threshold might be appropriate for assessments of the lack of changes during routine care. In addition, changes being equally likely to increase as decrease further suggests they reflect a routine variation. Finally, the grey area between having a relevant response and lack thereof depends on the intervention. This is particularly apparent in the surfactant intervention period, where there is no grey area between the 25% and 10% thresholds. Speculation suggests that the absolute level of change might also be a factor. The relative importance of false negatives and false positives, required for the intended use, should also be considered for each application. These all need further investigation and refinement.

Our prospectively defined thresholds for relevant change (25% and 50%) and lack thereof (10% and 5%) seem consistent with these data from these two populations and correspondingly consistent with clinical practice. Of course, monitoring the changes in PF-ratio to assess changes in oxygenation is a point of care imperative; nevertheless, reducing morbidity and mortality is the therapeutic goal. It is well understood that excessive or inadequate oxygenation has important long-term sequelae. Therefore, determining the impact of different changes on clinical outcomes is a most important issue and certainly much more complex.

One potential limitation of this work is that it reflects blood gas analyses, the timing of which certainly impacts the interpretation. While many samples may be drawn based on a standing order, blood gas measurements are often made associated with a clinical exacerbation. The timing of the measurements was protocolized by design, so it is not a problem with this analysis. However, a limitation of using change in PF-ratio. Also, the analysis only looked at change over 24 hours. The trend of measurements during the interim period of the pooled data reflects a potentially relevant change over a shorter time. Continuous monitoring with SpO_2 and FiO_2 (SF-ratio) might better picture the changing clinical situation. This would offer a continuous assessment of the impact of an intervention. However, the validity of SF-ratio as a measure of PF-ratio should be validated when used in this context. Nevertheless, SF-ratio is a good substitute for PF-ratio in categorizing the severity of respiratory distress [4]. It is also commonly used to assess lung

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recruitment maneuvers. Thus the prospect is promising.

This initial exploratory analysis has by its nature many additional limitations, each appropriate for evaluation in further studies. It is a small sample of two specific clinical situations. Using the change in oxygenation normalized for FiO_2 has potential uses both in routine care and investigations of the effectiveness of therapeutic interventions. In addition, the direction of change and magnitude of change should also be further evaluated.

Conclusions

This initial analysis supports the premise that considering the percent change in the PF-ratio can add to the understanding and communication of oxygenation response and stability. We expect it will stimulate further investigation.

Acknowledgments

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