Prediction of arterial oxygen partial pressure after changes in $F_{1O_2}$: validation and clinical application of a novel formula

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Background. Existing methods allow prediction of $P_{aO_2}$ during adjustment of $F_{1O_2}$. However, these are cumbersome and lack sufficient accuracy for use in the clinical setting. The present studies aim to extend the validity of a novel formula designed to predict $P_{aO_2}$ during adjustment of $F_{1O_2}$, and to compare it with the current methods.

Methods. Sixty-seven new data sets were collected from 46 randomly selected, mechanically ventilated patients. Each data set consisted of two subsets (before and 20 min after $F_{1O_2}$ adjustment) and contained ventilator settings, pH, and arterial blood gas values. We compared the accuracy of $P_{aO_2}$ prediction using a new formula (which utilizes only the pre-adjustment $P_{aO_2}$ and pre- and post-adjustment $F_{1O_2}$) with prediction using assumptions of constant $P_{aO_2}/F_{1O_2}$ or constant $P_{aO_2}/P_{aO_2}$. Subsequently, 20 clinicians predicted $P_{aO_2}$ using the new formula and using Nunn’s isoshunt diagram. The accuracy of the clinician’s predictions was examined.

Results. The 95% limits of agreement (LA95%) between predicted and measured $P_{aO_2}$ in the patient group were: new formula 0.11 (2.0) kPa, $P_{aO_2}/F_{1O_2}$ - 1.9 (4.4) kPa, and $P_{aO_2}/P_{aO_2}$ - 1.0 (3.6) kPa. The LA95% of clinicians’ predictions of $P_{aO_2}$ were 0.56 (3.6) kPa (new formula) and -2.7 (6.4) kPa (isoshunt diagram).

Conclusions. The new formula’s prediction of changes in $P_{aO_2}$ is acceptably accurate and reliable and better than any other existing method. Its use by clinicians appears to improve accuracy over the most popular existing method. The simplicity of the new method may allow its regular use in the critical care setting.

Keywords: intermittent positive-pressure ventilation; oxygen; oxygen inhalation therapy; pulmonary gas exchange; ventilation–perfusion ratio

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Mechanical ventilator (MV) adjustment is common practice in intensive care units (ICUs). Its primary objective is to achieve adequate organ O$_2$ supply and CO$_2$ clearance through maintaining appropriate arterial blood gas (ABG) values. Ventilator adjustment episodes commonly are based on and evaluated by arterial blood gas (ABG) analysis.

In order to minimize ABG analysis thus places a drain on health service resources.

Editor’s key points

- Ventilator adjustment during intensive care treatment is commonly based on and evaluated by arterial blood gas (ABG) analysis.
- In order to minimize ABG analysis, the present studies extended the validity of a novel formula designed to predict $P_{aO_2}$ during adjustment of $F_{1O_2}$.
- The authors found that its use by clinicians appears to improve accuracy over the most popular existing method.
- The simplicity of the new method may allow its regular use in the critical care setting.

In an attempt to minimize arterial gas analysis, and in an attempt to streamline ventilator management and accelerate attainment of the desired $P_{aO_2}$, there has arisen an array of methods aimed at predicting $P_{aO_2}$. One such technique, the isoshunt diagram, uses the concept of isoshunt lines where these virtual lines are used to relate $F_{1O_2}$ to $P_{aO_2}$; although this methodology is considered a ‘gold standard’ in terms of popularity and perceived accuracy, the method is too cumbersome to be of practical and frequent use in the critical care setting. Several mathematical formulae have been created in the past for use in the ICU to predict $P_{aO_2}$ after adjustment of fractional inspired oxygen ($F_{1O_2}$). All such formulae have been based on the assumption that the ratio of $P_{aO_2}$ to alveolar or inspired oxygen tension ($P_{aO_2}/P_{aO_2}$ or $P_{aO_2}/F_{1O_2}$) remains stable despite changing $F_{1O_2}$. Therefore, in such formulae, the calculated $P_{aO_2}/P_{aO_2}$ or $P_{aO_2}/F_{1O_2}$ ratio is used as a multiplier to predict resulting $P_{aO_2}$. However, the assumption of the constancy of
Prediction of arterial oxygen tension

Recently, we developed a novel formula to predict the resulting \( P_{aO_2} \); preliminary validation was promising. In this paper, we describe one study with three aims, each using a different methodology. In the first aim, we extend the clinical validation of the new formula using a new clinical data set. In the second, we compare its accuracy and consistency with the use of \( P_{aO_2} / FIO_2 \) and \( P_{aO_2} / P_{aCO_2} \). In the third, we test the use of the new formula by clinicians on the ICU in real-world, clinical scenarios against the current ‘gold-standard’ method (the isoshunt diagram).

**Methods**

**Clinical validation of the new formula**

Ethics approval was obtained from the local hospital ethics committee, who informed us that written consent from patients or their representatives was not necessary given that the trial involved no intervention on patients and no modification of their treatment.

Data were collected from randomly selected patients receiving mechanical ventilation in ICU. Patients who were haemodynamically unstable (mean arterial pressure \(< 60\) or \(> 110\) mm Hg, or heart rate \(< 50\) or \(> 120\) beats min\(^{-1}\)) or significantly anaemic (haemoglobin (Hb) \(< 8\) g dl\(^{-1}\)) were excluded. No patient was excluded on the basis of diagnosis. After exclusions, there remained 110 patients for study; the first 64 recruited patients were included in the first data set which has been published in a preliminary report. In this study, we recruited a further 46 patients to extend the validation. All patients were sedated and some had spontaneous breath in addition to the machine delivered breaths. A variety of ventilatory modes was used, including volume-controlled, pressure-controlled, and pressure-support ventilation.

Each patient's admission diagnosis, height, weight, age, and gender were recorded. Sixty-seven data sets were collected from the 46 patients during \( FIO_2 \) adjustments that formed part of their routine management (i.e. routine optimization of \( FIO_2 \) to attain appropriate \( P_{aO_2} \) in day-to-day management). Each data set comprised ventilator parameters (including \( FIO_2 \) measured by the internal oxygen analyzer of the Dräger Evita™ 4: Dräger Medical Inc., Luebeck, Germany), body temperature, Hb concentration, and ABG before and 20 min after \( FIO_2 \) adjustment.

Immediately before the \( FIO_2 \) adjustment and 20 min after, arterial blood samples were obtained using a 1 ml heparinized Micro ABG™ syringe (Marquette Medical Products, USA), after aspiration of 2 ml of blood. The samples were stored in crushed ice, thoroughly mixed, and the first drops were discarded; analysis was conducted within 3 min of sampling using a Roche Omni™ C blood gas analyzer (Roche Diagnostics, Germany), which ran one- and two-point calibrations every 30 min and 8 h, respectively. Quality control samples were run every 8 h. For any parameter out of range, a one-point system calibration was conducted and the same quality control sample was run again.

The value of \( P_{aO_2} \) after adjustment of \( FIO_2 \) was predicted using the new formula [equation (1)] and using established formulae that assume the constancy of \( P_{aO_2} / FIO_2 \) and \( P_{aO_2} / P_{aCO_2} \) during changing \( FIO_2 \) [equations (2) and (3), respectively].

The formulae used for the prediction of \( P_{aO_2} \) after adjustment of \( FIO_2 \) were:

\[
new P_{aO_2} = \frac{new FIO_2 \times old P_{aO_2}}{old FIO_2} \times \left[ 1 - \frac{(old FIO_2 - new FIO_2)}{2} \right] \]  
(1)

\[
new P_{aO_2} = \frac{new FIO_2 \times old P_{aO_2}}{old FIO_2} \]  
(2)

\[
new P_{aO_2} = \frac{new P_{aO_2} \times old P_{aO_2}}{old P_{aO_2}} \]  
(3)

where ‘old’ indicates a value before adjustment of \( FIO_2 \) and ‘new’ indicates a value after adjustment of \( FIO_2 \).

\[
P_{aO_2} = (P_B - P_{H_2O}) \times FIO_2 - 1.25 \times P_{aCO_2} \]  
(4)

where \( P_B \) is barometric pressure (101.3 kPa) and \( P_{H_2O} \) the saturated vapour pressure of water at 37°C (6.3 kPa); for each patient, calculations were performed assuming constant \( P_{aCO_2} \).

**Application of the new formula in clinical settings**

Twenty-six respiratory therapists (RTs) were invited to participate in the study. All RTs were active in the daily management of mechanically ventilated patients in critical care settings. Those who had < 1 yr experience in critical care were excluded. Of the 26 RTs approached, 20 gave their consent for participation.

The new formula [equation (1)] and the isoshunt diagram were presented and explained during a 1 h PowerPoint presentation (available from the corresponding author). The presentation addressed the theory behind each tool, the main features of each tool, how each worked, and their correct application in clinical settings. Participants were given time to practice using both tools on a clinical data set. Participants’ performance was reviewed by the researcher (H.M.A.-O.). Any misunderstanding was addressed individually. This process continued until all participants performed in a satisfactory manner.

The next day, a facilitator introduced the data collection form and ensured that all required data entries were completed. Twenty data sets were randomly selected from the above-mentioned pool of clinical data. No data sets were used that had been used in the previous day’s training exercise. Each data set comprised ventilator parameters before and after \( FIO_2 \) adjustment and ABG values before \( FIO_2 \) was changed. RTs were asked to predict the \( P_{aO_2} \) resulting from...
the change in $F_{O_2}$. Facilitators and participants were blinded to patients’ responses after $F_{O_2}$ adjustment. Participants were asked to view each data set as one isolated scenario. There was no time limit for completion of the data collection form.

**Statistical analysis**

The difference between $P_{A_{02}}$ before and after $F_{O_2}$ adjustment was calculated; this is termed the measured change. The difference between $P_{A_{02}}$ before $F_{O_2}$ adjustment and the predicted value was calculated; this is termed the predicted change. Bias in prediction was calculated as the difference between the measured and predicted magnitude of change in $P_{A_{02}}$ (i.e. using absolute values, removing the cancelling-out effect of under- and over-prediction). The 95% limits of agreement (LA95%) were calculated as bias ($k$)×standard deviation ($SD$),$^{24}$ with $k$ calculated from the $z$-distribution, where $k=2.086$ for $n=20$, $k=2.0$ for $n=67$, and $k=1.96$ for $n=173$. Data processing and charting were performed in Microsoft™ Excel (Office, 2007). All data are presented as mean ($SD$) unless stated otherwise.

**Results**

**Validation using the new data set and comparison with existing formulae**

In total, 67 data sets were collected from 46 patients. The mean measured magnitude of change ($SD$) in $P_{A_{02}}$ in the 67 data sets was 10.3 (10) kPa. The mean magnitude of change ($SD$) predicted by the new formula [equation (1)] was 10.4 (10.2) kPa. The mean magnitude of change predicted by the $P_{A_{02}}/F_{O_2}$ formula [equation (2)] was 8.4 (8) kPa. The mean magnitude of change predicted by the $P_{A_{02}}/P_{A_{02}}$ formula [equation (3)] was 9.3 (8.5) kPa.

The LA95% between measured and predicted magnitudes of change in $P_{A_{02}}$ were:

- new formula [equation (1)]: 0.11 (2.0) kPa;
- $P_{A_{02}}/F_{O_2}$ formula [equation (2)]: −1.9 (4.4) kPa;
- $P_{A_{02}}/P_{A_{02}}$ formula [equation (3)]: −1.0 (3.6) kPa.

**Global validation (combined data sets)**

Combining our previously published validation$^{21}$ with the present data set yields a large validation data pool (173 data sets). Table 1 shows patients’ details and diagnosis on admission. Patients had a variety of pathologies commonly seen in the ICU. Some patients suffered from two or more pathologies. Table 2 shows the average of patients’ MV characteristics and ABG values before $F_{O_2}$ adjustment and 20 min after. On 155 occasions, $F_{O_2}$ decreased [mean ($SD$): 0.61 (0.21) to 0.46 (0.13)]. On 18 occasions, it increased [mean ($SD$): 0.50 (0.18) to 0.65 (0.20)].

Figure 1a shows the bias and LA95% between measured and predicted magnitudes of change in $P_{A_{02}}$ using the new formula [equation (1)] 0.1 (2.0) kPa. Figure 1b shows the LA95% between measured and predicted magnitudes of change in $P_{A_{02}}$. On 22 August 2018 by guest

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**Table 1** Patients’ descriptive details and diagnoses. Data are presented as mean (range) for age, or mean (SD), unless otherwise stated. ARF, acute respiratory failure; ARDS, adult respiratory distress syndrome; CVA, cerebral vascular accident; post-CABG, post-coronary artery bypass graft; post-MVR, post-mitrval valve replacement; post-AVR, post-aortic valve replacement; others, chronic obstructive pulmonary disease, post-ventriculart septal defect closure, end-stage renal disease, hypothyroidism, post-craniotomy, and road traffic accident

| Age (yr) | 57 (37–79) |
| Gender (♂/♀) | 78/32 |
| Height (cm) | 164 (9.4) |
| Weight (kg) | 75 (21) |
| ARF (n) | 7 |
| Pneumonia (n) | 4 |
| ARDS (n) | 4 |
| Pulmonary oedema (n) | 4 |
| CVA (n) | 2 |
| Cardiac arrest (n) | 2 |
| Post-CABG (n) | 62 |
| Post-MVR (n) | 14 |
| Post-AVR (n) | 5 |
| Others (n) | 6 |

**Table 2** Characteristics of ventilation and gas exchange before and 20 min after MV adjustment (n=173); data are presented as mean (SD). $F_{O_2}$, inspired fraction of oxygen; $V_t$, tidal volume; $V_{E}$, minute ventilation; PEEP, positive end expiratory pressure; $P_{ACO_2}$, arterial partial pressure of carbon dioxide; $P_{A_{02}}$, arterial partial pressure of oxygen; $HCO_3$, bicarbonate concentration; $Hb$, haemoglobin concentration; $Sa_{02}$, arterial oxygen saturation; $P_{A_{02}}$, arterial partial pressure of oxygen; $P_{A_{02}}/P_{A_{02}}$, ratio of arterial to alveolar partial pressure of oxygen (dimensionless); $P_{A_{02}}/F_{O_2}$, ratio of arterial partial pressure of oxygen to inspired fraction of oxygen

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before adjustment</th>
<th>After adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_{O_2}$</td>
<td>0.6 (0.21)</td>
<td>0.48 (0.15)</td>
</tr>
<tr>
<td>Ventilatory frequency (bpm)</td>
<td>12 (3)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>$V_t$ (ml)</td>
<td>597 (123)</td>
<td>591 (125)</td>
</tr>
<tr>
<td>$V_{E}$ (litre min$^{-1}$)</td>
<td>7.3 (2.1)</td>
<td>7.1 (2.1)</td>
</tr>
<tr>
<td>PEEP (cm H2O)</td>
<td>6 (1.7)</td>
<td>6 (1.6)</td>
</tr>
<tr>
<td>pH</td>
<td>7.4 (0.07)</td>
<td>7.4 (0.06)</td>
</tr>
<tr>
<td>$P_{ACO_2}$ (kPa)</td>
<td>5.3 (8.8)</td>
<td>5.2 (8.8)</td>
</tr>
<tr>
<td>$P_{A_{02}}$ (kPa)</td>
<td>25 (15)</td>
<td>17.6 (7.3)</td>
</tr>
<tr>
<td>$HCO_3$ (mEq litre$^{-1}$)</td>
<td>24.3 (3.4)</td>
<td>24.1 (3.6)</td>
</tr>
<tr>
<td>$Hb$ (g dl$^{-1}$)</td>
<td>10.6 (1.9)</td>
<td>10.6 (1.8)</td>
</tr>
<tr>
<td>$Sa_{02}$ (%)</td>
<td>98 (1.7)</td>
<td>98 (1.9)</td>
</tr>
<tr>
<td>$P_{A_{02}}$ (kPa)</td>
<td>50.4 (19.7)</td>
<td>38.9 (14.7)</td>
</tr>
<tr>
<td>$P_{A_{02}}/P_{A_{02}}$</td>
<td>0.50 (0.19)</td>
<td>0.49 (0.18)</td>
</tr>
<tr>
<td>$P_{A_{02}}/F_{O_2}$ (kPa)</td>
<td>41.3 (15.9)</td>
<td>38.5 (13.9)</td>
</tr>
</tbody>
</table>
change in \(P_{aO_2}\) using the \(P_{aO_2}/F_{IO_2}\) formula [equation (2)] – 1.6 (4) kPa. Figure 1C shows the \(L_{A95}\%\) between measured and predicted magnitudes of change in \(P_{aO_2}\) using the \(P_{aO_2}/P_{AO_2}\) ratio formula (\(n=173\)). The dotted lines represent the bias and \(L_{A95}\%\) between the measured and predicted magnitude of change in \(P_{aO_2}\).

**Application of the new formula in clinical settings**

All participating RTs predicted \(P_{aO_2}\) for the 20 data sets presented, using the new formula [equation (1)] and the isoshunt diagram. The mean (sd) of the measured magnitude of change in \(P_{aO_2}\) was 6 (6.5) kPa. The mean (sd) of the predicted magnitude of change was 6.5 (7.1) kPa using the new formula [equation (1)] and 3.1 (5.1) kPa using the isoshunt method. \(L_{A95}\%\) between the measured and predicted magnitude of change using the new formula [equation (1)] was 0.6 (3.6) kPa (Fig. 2A); \(L_{A95}\%\) using the isoshunt diagram was – 2.7 (6.4) kPa (Fig. 2A).
Discussion

The present data suggest that the new formula [equation (1)] possesses sufficient accuracy to be used in clinical settings. Unlike the $P_aO_2 / FIO_2$ formula [equation (2)] and the $P_aO_2 / P_AO_2$ formula [equation (3)], it slightly overestimated the magnitude of $P_aO_2$ changes, whereas both the $P_aO_2 / FIO_2$ formula was more accurate than the $P_aO_2 / P_AO_2$ formula. Our new formula appears substantially more accurate (having smaller bias) and consistent (having narrower LA95%) than either in the current usage. In real clinical settings, clinicians achieved much worse accuracy using the isoshunt diagram compared with the new formula. This suggests that the new formula can be effectively applied in clinical settings and is an improvement on the tools currently available.

Several studies have explored the stability of the $P_aO_2 / FIO_2$ ratio in relation to $FIO_2$ changes and physiological shunt. Results of some such studies have been controversial. One study suggests that a $P_aO_2 / FIO_2$ ratio of $<$26.7 (kPa) correlates well with an intrapulmonary shunt fraction ($Qsp/Qt$) of $>$20%. The authors thus argue that the $P_aO_2 / FIO_2$ ratio can be used to quantify $Qsp/Qt$. Another study found that the $P_aO_2 / FIO_2$ ratio is comparable with the $P_aO_2 / P_AO_2$ ratio in terms of $Qsp/Qt$ reflection. Against such evidence, one study found that the $P_aO_2 / FIO_2$ ratio was an unreliable reflection of pulmonary shunt in a study of patients with adult respiratory distress syndrome; however, the same study found the $P_aO_2 / FIO_2$ ratio the least sensitive to $FIO_2$ modifications among other oxygen-based indices. Other studies suggest that the $P_aO_2 / FIO_2$ ratio resists variation induced by varying $FIO_2$ only in patients where true shunt is predominant.

Regardless of whether the ratio is a stable indicator of pulmonary oxygenation, such does not appear to affect its utility as a predictor of $P_aO_2$. Evidence suggests that the behaviour of the $P_aO_2 / FIO_2$ ratio parallels that of $P_aO_2$ in response to $FIO_2$ adjustment. A mathematical correction factor was derived (from basic mathematical and physiological theory) to ‘flatten’ the curve of $P_aO_2 / FIO_2$ vs $FIO_2$, removing the non-linearity and rendering $P_aO_2$ more predictable. A more complex correction factor was avoided for the sake of acceptable simplicity for clinical use.

Validity study data suggest that predictions using the new formula have acceptable accuracy over a wide range of $FIO_2$. It appears more accurate and precise (i.e. has smaller bias and narrower LA95%) than predictions assuming the

Fig 2 LA95% between the measured magnitude of change in $P_aO_2$ and that predicted by recruited RTs using (a) the new formula and (a) the isoshunt diagram ($n$=20). The dotted lines represent the bias and LA95% between measured and predicted magnitude of changes in $P_aO_2$. 
Prediction of arterial oxygen tension

constancy of \( P_{A0} / IF_{10} \) and \( P_{A0} / P_{AO} \) formulae. Predictions using the \( P_{A0} / IF_{10} \) and \( P_{A0} / P_{AO} \) formulae tend to underestimate the magnitude of change in \( P_{A0} \), particularly after large change in \( F_{10} \). This finding contradicts previous findings that the \( P_{A0} / P_{AO} \) ratio tends to overestimate the magnitude of change in \( P_{A0} \). This, in evidence suggests that a biphasic evolution of the \( P_{A0} / P_{AO} \) ratio against \( F_{10} \) (especially at lower ranges) may be responsible for the over-estimation of \( P_{A0} \). Such behaviour seems not to have a major impact on predictions using the \( P_{A0} / P_{AO} \) formula.

Comparisons with other existing formulae are difficult. This is due to different statistical approaches used by different researchers. It has been common for researchers to present coefficients of correlation between measured and predicted values as measures of the quality of prediction of measured values. However, a large correlation coefficient in this context does not necessarily reflect a good agreement. The \( LAIO50 \) provides a better quantification of the agreement between predicted and measured \( P_{A0} \) than does simple correlation.

One may postulate possible causes of deviation from the line of equality by the new formula. There may be coincidental changes in a patient’s pathophysiology during the equilibrium period; it may also be because of errors in automated ABG analysis, especially of values outside the calibration ranges; it may also arise from spontaneous (and therefore unpredictable) variation in \( P_{A0} \). All three factors, in all likelihood, have some effect. However, spontaneous variation in \( P_{A0} \) appears especially likely; \( P_{A0} \) is known to vary spontaneously in apparently stable patients from 0.1 to 6 (kPa). Such factors would not only disrupt the predictive accuracy of the new formula; they would disrupt the accuracy of any formula. Further, the new formula was tested on mechanically ventilated patients that were clinically and haemodynamically stable; patients with unstable pathophysiological states may not reproduce similar findings.

The ability of clinicians to apply the new formula in real scenarios suggests that it is a promising tool for use in clinical settings. Clinicians reported anecdotally that using it was easy, and compared favourably with the ‘gold standard’ of the isoshunt diagram. In real clinical settings, the use of the new formula appears to provide more accurate and more consistent prediction than the current ‘gold standard’ method. The present investigation suggests that application of Nunn’s virtual shunt lines in clinical scenarios can be inaccurate, misleading, or both. Inaccurate estimation of resulting \( P_{A0} \) might be caused by several assumptions in the virtual shunt model. It may also stem from incapability of clinicians to apply the isoshunt method correctly; clinicians may face difficulty to precisely define the appropriate \( P_{A0} \) values. In fact, the authors of the isoshunt diagram have acknowledged that small errors at lower \( P_{A0} \) values would produce considerable error in the estimation of the shunt line and hence the resulting \( P_{A0} \). Such technical deficits may reduce the value of the use of virtual shunt lines in clinical settings.

In conclusion, the new formula combines ease of use and sufficient accuracy to be used in critical care settings for predicting \( P_{A0} \) during adjustment of \( F_{10} \). The present data proved its value on stable mechanically ventilated patients. Its ease of use makes it a convenient alternative to the existing methods. Of course, it will not obviate the need for ABG analysis, which may inform clinicians of other important data, such as acid–base status. Further studies might be necessary for different patients’ populations.

Conflict of interest

J.G.H. is an editor and editorial board member of the British Journal of Anaesthesia.

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