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Validation and application of a high-fidelity, computational model of acute respiratory distress syndrome to the examination of the indices of oxygenation at constant lung-state

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Background. Calculated venous admixture (Qs/Qt) is considered the best index of oxygenation; surrogates have been developed (Pao₂/FIO₂, respiratory index, and arterioalveolar P O₂ difference), but these vary with FIO₂, falsely indicating a change in lung-state. Using a novel model, we aimed to quantify the behaviour of the indices of oxygenation listed above during physiological and treatment factor variation. The study is the first step in developing an accurate and non-invasive tool to quantify oxygenation defects.

Methods. We present the static and dynamic validation of a novel computational model of gas exchange in acute respiratory distress syndrome (ARDS) based upon the Nottingham Physiology Simulator. Arterial gas tension predictions were compared with data derived from ARDS patients. The subsequent study examined the indices’ susceptibility to variation induced by independent changes in FIO₂ (0.3–1.0), haemoglobin concentration (Hb: 6–14 g dl⁻¹), oxygen consumption (VO₂: 250–350 ml min⁻¹), and Paco₂ (4–8 kPa).

Results. Static validation produced a mean error of −0.3%, a 10-fold improvement over previous models. Dynamic validation produced a mean prediction error of −0.05 kPa for Pao₂ and 0.09 kPa for Paco₂. Every parameter, especially FIO₂, induced variation in all indices. The least FIO₂-dependent index was Qs/Qt (variation: 5.1%). In contrast, Pao₂/FIO₂ varied by 77% through the range of FIO₂.

Conclusions. We have improved simulation of gas exchange in ARDS by using a sophisticated respiratory model. Using the validated model, we have demonstrated that the current indices of oxygenation vary with alteration in Hb, Paco₂, and VO₂ in addition to their previously well-documented dependence on FIO₂.

Br J Anaesth 2008; 101: 358–65

Keywords: lung, respiratory distress syndrome; measurement techniques, gas exchange; measurement techniques, lung shunting; model, computer simulation; model, respiratory failure

Accepted for publication: May 2, 2008

On a daily basis, clinicians use patients’ arterial gas tensions to communicate and interpret the severity of gas exchange defects; however, these values are dependent upon factors outside the patient’s lungs, such as inspired oxygen fraction (FIO₂), minute ventilation, and oxygen consumption, meaning that arterial gas tensions must be viewed in the context of other physiological values and the treatment provided. For many years, clinicians have sought to describe patients’ oxygenation without reliance on such contextual descriptors. Fortunately, the complexity of the human lung’s ventilation–perfusion (VQ) and the behaviour of whole blood, all integrated with a dynamic and autoregulating cardiovascular system, cannot easily be described. Thus, the tension-based indices of oxygenation (i.e. Pao₂/FIO₂, respiratory index, and arterioalveolar P O₂ difference) are not as reliable as the gold standard, content-based venous admixture (Qs/Qt). In particular, the tension-based indices vary as factors outside the patient’s pathophysiology change, falsely implying a change in the patient’s lung-state.
This has far-reaching implications as the indices of oxygenation are used for communicating and monitoring a patient’s illness severity, assessing the efficacy of interventions, stratification for research purposes, resource allocation, and determination of clinical management pathways. However, the continued popularity of the tension-based indices must be due, in part, to the fact that \( Q_s/Q_t \) calculation requires mixed venous blood sampling via a pulmonary artery catheter, which is not without risk.\(^{13} \) Therefore, there is a need for an accurate, clinically useful, and non-invasive tool to quantify patients’ lung-states.

The use of simulated acute respiratory distress syndrome (ARDS) lung provides opportunities for research unavailable using standard clinical approaches. In 2001, Hahn\(^{14} \) called for a detailed investigation of this issue using sophisticated modelling; in particular, hypoxic pulmonary vasoconstriction (HPV) and tidal ventilation were regarded as essential but, at the time, missing. The Nottingham Physiology Simulator (NPS) is a sophisticated computational multi-compartmental lung model that incorporates tidal ventilation, pulsatile pulmonary blood flow, HPV, and a realistic and validated oxygen–haemoglobin model.\(^{15–17} \)

Our intention was to validate and apply an NPS ARDS lung model to an assessment of the behaviour of the current indices of oxygenation during variation in diverse physiological factors within the model; these included haemoglobin concentration, oxygen consumption, inspired oxygen concentration, and arterial CO\(_2\) tension. The study represents the first step in a programme of work intended to produce a robust index of oxygenation whose calculation does not require mixed-venous blood sampling.

Methods

The Nottingham Physiology Simulator

The NPS has been validated in a number of situations and configurations.\(^{15–20} \) The principles underlying the modelling are summarized in the appendix (see Supplementary material at British Journal of Anaesthesia online).

NPS version 060406 was used in this investigation and it is available for download via the corresponding author.

Model calibration

A detailed description of the model configuration and validation exercise is available in the appendix (see Supplementary material at British Journal of Anaesthesia online).

The ARDS VQ defect was calibrated in the NPS using data published by Nirmalan and colleagues\(^7 \) in 2001; in this investigation, the authors measured arterial and mixed venous gas tensions, haemoglobin concentration, and cardiac output in 10 patients known to have ARDS. The NPS ARDS model VQ defect was configured using the 10 data sets from Patients 3 and 4. These patients were randomly selected and subsequently excluded from the validation investigation. The data set from two patients was considered adequate to configure the model VQ defect; this allowed validation against the remaining eight patients’ data.

Model validation

In brief, a static validation of the configured NPS model was performed using the remaining 45 data sets (Patients 1, 2, 5, 6, 7, 8, 9, and 10) from Nirmalan’s study. Within-subject and whole-group \( P_aO_2 \) prediction errors were calculated.

Subsequently, a dynamic validation of the configured NPS model was performed using published data on ARDS patient responses to changing \( F_{io2} \), respiratory rate (RR), and tidal volume (Tv).\(^{15} \) For the purposes of validation, the quality of matching was judged by the error in predicting the resulting \( P_aO_2 \) and \( P_aCO_2 \).

Evaluation of indices of oxygenation

The values of tidal volume, RR, PEEP, and inspiratory to expiratory ratio were chosen to represent typical ARDS patients.\(^7 \)\(^{13} \)\(^{21} \) HPV and dynamic oxygen–haemoglobin association–dissociation were enabled within the model.

The following indices of oxygenation were evaluated in this investigation: calculated shunt fraction (\( Q_s/Q_t \)), alveolar–arterial oxygen tension gradient (\( P_{aO_2} - a_{O_2} \)), respiratory index (\( P_{aO_2} - a_{O_2} / P_aO_2 \)), and PF ratio (\( P_{aO_2}/F_{io2} \)).

Each index was recorded in a virtual patient with the configured VQ defect held constant (Table 1). The inspired oxygen concentration (\( F_{io2} \)), haemoglobin concentration (Hb), arterial carbon dioxide tension (\( P_aCO_2 \)), and oxygen consumption (\( V_O_2 \)) were varied in isolation, whereas the other variables were clamped (held constant) at baseline (Table 2). Alveolar oxygen tension (\( P_aO_2 \)) was calculated using the alveolar gas equation and arterial oxygen tension (\( P_{aO_2} \)) and mixed venous oxygen tension (\( P_{vO_2} \)) were recorded.

Tidal volume (Vt) and RR were constant throughout the investigation (Table 1), thus keeping lung-state constant. Respiratory exchange ratio (RER) was kept constant except to induce change in (or maintain) \( P_{aCO_2} \) while \( V_O_2 \) was altered.

| Weight | 70 kg |
|---|---|
| Inspired gas | Warmed and humidified |
| Inspiratory flow pattern | Constant flow |
| Tidal volume | 6 ml kg\(^{-1} \) |
| Respiratory rate | 15 bpm |
| PEEP | 9.5 cm H\(_2\)O |
| Inspiratory to expiratory ratio | 1:2 |
| Respiratory exchange ratio | 0.8 |
| Cardiac output | 9.5 litre min\(^{-1} \) |
| Base excess | 0 mmol litre\(^{-1} \) |

Table 1 NPS configuration for the virtual patient used in this investigation. RER varied between 0.47 and 1.03 to maintain \( P_{aCO_2} \) during variation in \( V_O_2 \) or alteration of \( P_{aCO_2} \) independent of other variables.
Comparison was made between the NPS model and the simpler pulmonary model of Nirmalan and colleagues. Model performances were assessed by comparing the predicted estimates with the measured $P_{aO_2}$ (kPa) values using within-subject Pearson correlation ($r$) and agreement was quantified using intraclass correlation (ri). Biases (predicted–measured) for actual and proportional errors in $P_{aO_2}$ data were estimated with 95% confidence intervals (CI) and within-subject 95% limits of agreement (LA). Error biases (proportional differences or prediction errors) were calculated as: (predicted value–measured value)/measured value. In addition, the data were subjected to regression analysis to estimate the within-subject 95% prediction intervals across the range of $P_{aO_2}$ values used in the validations. Analyses were carried out using Excel 2000 (Microsoft Inc., Redmond, WA, USA), Number Cruncher Statistical Software (NCSS 2004, Inc., Kaysville, UT, USA), and GraphPad Prism 4.03 (GraphPad Software Inc., San Diego, CA, USA).

### Results

#### Model calibration

The NPS ARDS VQ defect was configured by setting bronchial resistance vertical slider-1 to 400/2500 and vascular resistance vertical slider-5 to 16/2500. Sliders 1–5 on each scale represent the anatomical progression from lung apex to base, respectively. The resulting configuration of the NPS ARDS lung model incorporated a substantial

### Table 2

| Variable                  | Baseline | Examined range | Increment |
|---------------------------|----------|----------------|-----------|
| $F_{IO_2}$ (%)            | 50       | 30–100         | 10        |
| Haemoglobin (g dl$^{-1}$) | 8        | 6–14           | 2         |
| $P_{aCO_2}$ (kPa)         | 6        | 4–8            | 2         |
| $V_{O_2}$ (ml min$^{-1}$) | 300      | 250–350        | 50        |

Fig 1 Induced variation in alveolar, arterial, and mixed-venous oxygen tensions.
VQ defect and an absolute shunt of 40% of cardiac output. All other sliders stayed at their default settings of 1. This resulted in an average $P_{\text{aO}_2}$ prediction error against the calibration data set of 1.48% (SD 14.0%).

**Static validation**

Within-subject correlation coefficients ($r$) for measured and predicted $P_{\text{aO}_2}$ were 0.897 for the Nirmalan model and 0.903 for the NPS model. Overall agreements, as assessed by intra-class correlation coefficients ($r_i$) were 0.968 and 0.975, respectively, showing further improvements in model fit with the NPS model. The predicted–measured biases with 95% CI and within-subject 95% LA were $-0.58$ kPa (95% CI $-1.57$ to $0.41$, 95% LA $-2.89$ to $1.73$) and $-0.20$ kPa (95% CI $-1.13$ to $0.73$, 95% LA $-2.38$ to $1.98$) for the models, respectively. These represent error biases of $-3.0\%$ (95% CI $-9.3$ to $3.39$; 95% LA $-17.7$ to $11.7$) and $-0.3\%$ (95% CI $-5.7$ to $5.1$; 95% LA $-12.8$ to $12.2$), respectively, in favour of the NPS model. The within-subject SD of residuals of 1.11 and 1.07 kPa (representing the corresponding 95% prediction intervals of 2.18 and 2.10 kPa) for the models, respectively, show that differences in predicted and measured estimates are not clinically important.

**Dynamic validation**

The settings for extrapulmonary shunt and physiological dead space used to match the NPS ARDS model to patients before intervention are given in the appendix (Supplementary Table 3a). The post-intervention $P_{\text{aO}_2}$ and $P_{\text{aCO}_2}$ predicted by the NPS ARDS model are given in the appendix (Supplementary Table 2a). The mean magnitude of change observed in patients’ $P_{\text{aO}_2}$ after intervention was 6.05 kPa; the 95% CI of the error in predicting $P_{\text{aO}_2}$ was $-0.53$ to $0.43$ kPa (error bias $-0.05$ kPa). The mean magnitude of change observed in patients’ $P_{\text{aCO}_2}$ after intervention was 0.94 kPa; the 95% CI of the error in predicting $P_{\text{aCO}_2}$ was $-0.10$ to $0.27$ kPa (error bias 0.09 kPa).

**Evaluation of indices of oxygenation**

Variations in $P_{\text{aO}_2}$, $P_{\text{aCO}_2}$, and $P_{\text{vO}_2}$ induced by changing $Hb$, $F_{IO2}$, $P_{\text{aCO}_2}$, and $V_{O2}$ are presented in Figure 1. Variations in $P_{\text{aO}_2}/F_{IO2}$, $Qs/Qt$, $P_{A−aO_2}$, and $P_{A−aO_2}/P_{\text{aO}_2}$ induced by changing $Hb$, $F_{IO2}$, $P_{\text{aCO}_2}$, and $V_{O2}$ are presented in Figures 2–5, respectively. Maximal variation in each index is presented in Table 3.

Variation in $F_{IO2}$ caused the largest variation in each index; $Qs/Qt$ had the smallest $F_{IO2}$-induced variability of 5.1%,

![Graph](image1)

![Graph](image2)

![Graph](image3)

![Graph](image4)

**Fig 2** Induced variation in the PF ratio ($P_{\text{aO}_2}/F_{IO2}$) with constant pulmonary VQ configuration.
whereas $\text{PaO}_2/\text{FiO}_2$ varied by 77%. $\text{PaO}_2/\text{FiO}_2$ was also susceptible to variation induced by changing $\text{VO}_2$, Hb, and $\text{PaCO}_2$.

Induced changes were linear except in $\text{PaO}_2/\text{FiO}_2$ and $\text{PA}-\text{aO}_2/\text{PaO}_2$ during $\text{FiO}_2$ variation. Each of these indices was less prone to $\text{FiO}_2$-induced variation between $\text{FiO}_2$ 0.6 and 1.0; in this range, $\text{PaO}_2/\text{FiO}_2$ varied by 12.3% and $\text{PA}-\text{aO}_2/\text{PaO}_2$ varied by 16.3%.

**Discussion**

The two validation exercises generated a credible, high-fidelity model that can be applied reliably to the clinical context of ARDS throughout the relevant ranges of treatment and pathophysiological variation. The increased sophistication of the NPS model most likely explains its improved performance over that of Nirmalan and colleagues. The addition of HPV, tidal ventilation, pulsatile pulmonary blood flow, and dynamic oxygen–haemoglobin binding may reasonably be expected to make the model more credible and more life-like than earlier, simple models.

Using the validated NPS ARDS model, the current indices of oxygenation showed significant variability without a change in lung-state (Table 3), generating false impressions of the patient’s disease. Overall, the content-based $Qs/Qt$ varied the least, with $\text{PaO}_2/\text{FiO}_2$ performing the best among the less reliable tension-based indices. In particular, $\text{PaO}_2/\text{FiO}_2$ varied little within the ARDS-relevant range of $\text{FiO}_2$ 60–100%, which is in agreement with previous studies.

Previous modelling studies have indicated that Hb does not influence gas exchange in ARDS. However, in those investigations, $\text{PaO}_2$ and $\text{PV}_2$ were held unrealistically constant. In this study, a reduction in Hb decreased $\text{PV}_2$ in the shunt-rich NPS ARDS model. It is apparent that for a given $\text{PA}_2$, reduced $\text{PV}_2$ may induce diffusion-limitation of oxygen transfer, thereby reducing $\text{PaO}_2$. Therefore, haemoglobin concentration has a predictable effect on the calculated tension-based indices (Table 3) via this mechanism. In the same way, alterations in $\text{VO}_2$ caused changes in $\text{PV}_2$, and thus $\text{PaO}_2$. Although there was small variation in $\text{PA}_2$, the gradient of the line (Fig. 1) was almost identical to that of $\text{PaO}_2$, generating little variation in $\text{PA}-\text{aO}_2$.

Indices that incorporate $\text{PA}_2$ assume the equality of $\text{Paco}_2$ and $\text{PA}_2$, that is, $\text{Paco}_2$ is easily measurable and acts as a surrogate for $\text{PA}_2$ in the alveolar gas equation.
This assumption may not be appropriate within the ARDS lung. Indeed, unique values for $P_{A\text{O}_2}$ and $P_{A\text{CO}_2}$ do not exist; such averaged values inadequately represent areas of the lung that are poorly ventilated, perfused, or both. The variation of $P_{A\text{O}_2}$ with $P_{A\text{CO}_2}$ is explained by the NPS ARDS model’s dynamic oxygen–haemoglobin dissociation model; both Haldane and Bohr effects may be observed within the NPS. The incorporation into our ARDS model of a high-fidelity model of the dynamic relationship between oxygen and haemoglobin is crucially important, and represents an advance over previous investigations in this field.

In this investigation, we used a shunt-rich model of ARDS lung-state. However, in disease states with less absolute shunt (where perfused alveoli receive zero ventilation) and more venous admixture (where perfused alveoli receive inadequate but non-zero ventilation), both content- and tension-based indices are likely to behave quite differently from that observed in this study. Previous clinical and modelling investigations have shown a variable effect of $FIO_2$ on $Qs/Qt$. Plausible explanations for the apparent contradictions include blunting of HPV, absorption atelectasis, and the diversity of VQ distributions. Furthermore, previous studies have found that in the presence of smaller shunts and lower $FIO_2$, $P_{a\text{CO}_2}/FIO_2$ was dependent on $FIO_2$, thus rendering it misleading in clinical practice. This could be explained by the different responsiveness of $P_{a\text{O}_2}$ to changing $FIO_2$ in the presence of poorly ventilated compared with unventilated alveoli.

Despite the improvements over previous models of respiratory pathophysiology, the current study is limited in that the results are representative of a single virtual patient rather than a heterogeneous patient population. While our virtual patient subject is broadly representative of the ARDS population, compliant, impervious to harm, and free of ethical constraint, it is a single subject, and does not represent every lung-state; future modelling studies should aim to create virtual populations to allow the broader applicability of findings and a greater demonstration of model robustness.

In conclusion, we have improved simulation of gas exchange in ARDS by using a sophisticated non-linear respiratory model based upon the NPS. The increased sophistication of the NPS ARDS model has permitted physiological clamping, that is, the ability to hold a physiological parameter constant. Thus, we have shown that the indices of oxygenation also vary with alteration in Hb, $P_{a\text{CO}_2}$, and $V_\text{O}_2$ in addition to their well-documented
dependence on \(F_{\text{IO}_2}\); such dependence causes apparent changes in lung-state during alterations in physiological and treatment factors when no change in lung-state has occurred. Future work should examine the robustness of these indices in other pulmonary disease states and in the population variation seen within disease states. The factors that vary with external variation should now be isolated and mathematically ‘clamped’ so that we may develop new, independent indices of gas exchange and, in particular, oxygenation.

Supplementary material
Supplementary material is available at British Journal of Anaesthesia online.

Funding
This work was supported in part by a grant from the European Society of Anesthesiology.

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Table 3  Maximal induced variation, expressed as a percentage of the smallest observed value

| Parameter       | \(PaO_2/\text{FIO}_2\) | \(Qs/Qt\) | \(P_a-a_o\) | \(P_a-a_o/\text{PaCO}_2\) |
|-----------------|------------------------|-----------|-------------|--------------------------|
| Haemoglobin     | 34.6                   | 0.9       | 6.8         | 45.7                     |
| \(V_o\)         | 23.6                   | 1.0       | 0.7         | 24.1                     |
| \(P_a-o\)       | 22.0                   | 1.0       | 11.5        | 36.0                     |
| \(F_{\text{IO}_2}\) | 77.0                   | 5.1       | 405         | 165                      |

Fig 5 Induced variation in the respiratory index \((P_a-a_o)/P_aO_2)\) with constant pulmonary VQ configuration.
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