British Journal of Anaesthesia **101 (3):** 358–65 (2008)
doi:10.1093/bja/aen181 Advance Access publication June 20, 2008

BJA

CRITICAL CARE

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 (Pa_{O_2}/FI_{O_2}, respiratory index, and arterioalveolar PO_2 difference), but these vary with FI_{O_2}, 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 FI_{O_2} (0.3–1.0), haemoglobin concentration (Hb: 6–14 g dl^{-1}), oxygen consumption (VO_2: 250–350 ml min^{-1}), and Pa_{CO_2} (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 Pa_{O_2} and 0.09 kPa for Pa_{CO_2}. Every parameter, especially FI_{O_2}, induced variation in all indices. The least FI_{O_2}-dependent index was Qs/Qt (variation: 5.1%). In contrast, Pa_{O_2}/FI_{O_2} varied by 77% through the range of FI_{O_2}.

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, Pa_{CO_2}, and VO_2 in addition to their previously well-documented dependence on FI_{O_2}.

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 (FI_{O_2}), 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.[1–5]

Unfortunately, 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. Pa_{O_2}/FI_{O_2}, respiratory index, and arterioalveolar PO_2 difference) are not as reliable as the gold standard, content-based venous admixture (Qs/Qt).[4–12] 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 Pa_{O_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 FI_{O_2}, 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 Pa_{O_2} and Pa_{CO_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 ($PA{-}a_{O_2}$), respiratory index ($PA{-}a_{O_2}/Pa_{O_2}$), and PF ratio (Pa_{O_2}/FI_{O_2}).

Each index was recorded in a *virtual* patient with the configured VQ defect held constant (Table 1). The inspired oxygen concentration (FI_{O_2}), haemoglobin concentration (Hb), arterial carbon dioxide tension (Pa_{CO_2}), and oxygen consumption (VO_2) were varied in isolation, whereas the other variables were clamped (held constant) at baseline (Table 2). Alveolar oxygen tension (PA_{O_2}) was calculated using the alveolar gas equation and arterial oxygen tension (Pa_{O_2}) and mixed venous oxygen tension ($P\bar{v}_{O_2}$) 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) Pa_{CO_2} while VO_2 was altered.

Table 1 NPS configuration for the virtual patient used in this investigation. RER varied between 0.47 and 1.03 to maintain Pa_{CO_2} during variation in VO_2 or alteration of Pa_{CO_2} independent of other variables

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_2O
Inspiratory to expiratory ratio	1:2
Respiratory exchange ratio	0.8
Cardiac output	9.5 litre min^{-1}
Base excess	0 mmol $litre^{-1}$