1. INTRODUCTION

Choosing appropriate ventilator settings may be regarded as a balance between ensuring sufficient gas exchange whilst preventing ventilator induced lung injury (VILI). Achieving this balance can be difficult, partly due to changes in ventilator settings both improving gas exchange and at the same time increasing the risk of VILI. In the case of inspired oxygen fraction (FiO₂) increases can improve oxygenation but also increase risk of the effects of oxygen toxicity (Nash et al., 1967, Altemeier and Sinclair, 2007), and absorption atelectasis (Dantzker et al., 1975, Edmark et al., 2003).

Several computer systems have been developed to aid in ventilator management, these including the setting of FiO₂ (Rutledge et al., 1993, Shahsavar et al., 1995, Raemer et al., 1997, McKinley et al., 2001, Kwok et al., 2004, Tehrani et al., 2004, Rees et al., 2006). These systems can be divided into closed loop ventilator control systems (Raemer et al., 1997, Tehrani et al., 2004) and decision support systems (DSS) (Rutledge et al., 1993, Shahsavar et al., 1995, McKinley et al., 2001, Kwok et al., 2004, Rees et al., 2006). Closed loop ventilator control systems may be valuable when targets for the ventilator therapy have been defined, but do not provide assistance in setting the appropriate target for the individual patient.

Recent advances in DSS have focused on applying a rule-based approach, implementing the heuristics of clinicians either by automating clinical protocols (McKinley et al., 2001) or using fuzzy rule bases (Kwok et al., 2004). While such systems may indeed support management of ventilator therapy, they do not support the clinician in understanding the pathophysiology of the individual patient.

A DSS based on physiological models and utility theory provides both advice on the appropriate target, and provides physiological understanding. When physiological models are tuned to fit data for a particular patient, the model parameters describe the state of the patient, and the model can be used to simulate the outcome of changes in ventilator settings. Utility theory (Keeney and Raiffa, 1993) can be used to quantify the expected utility of outcomes, and when combined with physiological models, the ventilator settings associated with maximal expected utility can be located and provided as advice to the clinician.

The INVENT system (Rees et al., 2006) provides advice on setting FiO₂ and minute volume using physiological models of oxygen transport, carbon dioxide transport and lung mechanics combined with utility theory.

The purpose of this study was to retrospectively evaluate the advice provided by the INVENT system in intensive care patients. The physiological model of oxygen transport used to calculate advice on FiO₂, is identifiable from clinically available measurements (Rees et al., 2002), and has been shown capable of describing various patient types including intensive care patients (Kjærgaard et al., 2003). The advice on minute volume is dependent on all the three aforementioned models in INVENT. The mathematical model of lung mechanics currently applied in INVENT assumes a linear static compliance of the respiratory system. However, this is not sufficient to simulate the effects of changes in minute volume in intensive care patients with acute respiratory problems, where the compliance has been shown to be nonlinear (Matamis et al., 1984). As a first step, therefore, this article evaluates only the ability of INVENT to provide advice on setting FiO₂.
Fig. 1. Components of INVENT: INVENT FiO\textsubscript{2} advice is calculated in a feedback loop initiated with newly identified model parameters. The optimization component changes FiO\textsubscript{2} and the model simulates resulting oxygenation (arterial: SaO\textsubscript{2}, mixed venous: SmvO\textsubscript{2}). A total penalty is calculated from FiO\textsubscript{2}, SaO\textsubscript{2} and SmvO\textsubscript{2} and fed back to the optimization component. The optimal FiO\textsubscript{2} is that resulting in minimal total penalty.

2. METHODS

2.1 The INVENT system

Figure 1 illustrates the components of INVENT for providing advice on FiO\textsubscript{2}. The physiological model of oxygen transport is identified using a previously published parameter estimation method (Rees et al., 2002), fitting data describing arterial oxygen saturation (SaO\textsubscript{2}) and end tidal oxygen fraction (FetO\textsubscript{2}). This method yields two model parameters describing the patient’s pulmonary gas exchange status; shunt quantifies the amount of blood flowing through the lungs without reaching ventilated alveoli, and fA2 quantifies the degree of ventilation/perfusion mismatch in the lungs. When identified for a patient, the model can simulate the resulting oxygenation for a particular patient at any FiO\textsubscript{2}.

The optimization component varies FiO\textsubscript{2} to evaluate the utility associated with possible FiO\textsubscript{2} levels. For each FiO\textsubscript{2} value, the model simulates the corresponding arterial oxygen saturation (SaO\textsubscript{2}) and mixed venous oxygen saturation (SmvO\textsubscript{2}). SaO\textsubscript{2} and SmvO\textsubscript{2} are used to calculate the penalty associated with risk of ischemia. This penalty is calculated as the sum of penalty associated with risk of local ischemia and general ischemia calculated from SaO\textsubscript{2} and SmvO\textsubscript{2}, respectively (see A, Fig. 1). FiO\textsubscript{2} is used to calculate the penalty associated with risk of the effects of oxygen toxicity and with absorption atelectasis (see B, Fig. 1). The total penalty for a given FiO\textsubscript{2} is the sum of the penalty due to ischemia risk and the penalty due to risk of the effects of oxygen toxicity and absorption atelectasis. The FiO\textsubscript{2} value resulting in minimal total penalty is provided as advice to the clinician.

2.2 Data Collection

Eighteen patients with acute lung injury (ALI) were included in the study, 14 male and 4 female. Median age was 64.5 years (range 27-85) and weight 80 kg (range 70-140). The study was performed at the department of intensive care at Rigshospitalet (Copenhagen, Denmark). Patients were ventilated using a Servo 300 or a Servoi (Maquet A/B, Solna, Sweden). Nine patients were ventilated using controlled ventilation modes, either pressure regulated volume control or pressure control modes. Seven patients were ventilated using pressure support mode. Informed consent was obtained from nearest relative or legal guardian. The study was approved by the Ethical Committee of North Jutland and Viborg Counties and the Ethical Committee of Copenhagen.

After inclusion in the study the patient was connected to a Servoi ventilator dedicated for the study. FiO\textsubscript{2} and FetO\textsubscript{2} were measured side-stream by a paramagnetic oxygen analyser (Oxigráf, Mountain View CA, USA). Pulse oximetry oxygen saturation (SpO\textsubscript{2}) and arterial blood gases were measured using a stand alone respiratory monitor (CO\textsubscript{2}SMO Plus, Novametrix Medical Systems, Wallingford CT, USA). For each patient FiO\textsubscript{2} was modified in 4-6 steps to achieve oxygen saturations ranging from 88 % - 100 %, as previously described (Rees et al., 2002). When steady state was reached for each FiO\textsubscript{2} level, measurements were taken of ventilation volumes, SpO\textsubscript{2}, oxygen consumption, end tidal carbon dioxide fraction,
FiO$_2$ and FetO$_2$. In addition, an arterial blood sample was drawn at each FiO$_2$ level and analyzed to obtain blood gases, acid-base status, and concentrations of haemoglobins (pH, SaO$_2$, PaO$_2$, PaCO$_2$, Base excess, Hb, HbMet and HbCO) (Radiometer ABL 700, Copenhagen, Denmark).

Two patients were excluded from the study due to malfunction of the data collection software. For the remaining 16 patients data from the experiments could be used for analysis. In 11 patients measurements of pulmonary gas exchange were performed at 2 different settings of PEEP. Therefore a total of 27 patient cases were used in the study.

2.3 Retrospective evaluation of INVENT

Several steps were taken to evaluate the value of FiO$_2$ suggested by INVENT:

The oxygen model was fitted to measurements of respiration and arterial oxygenation as described above. Measurements of arterial oxygenation at different FiO$_2$ levels were taken from a pulse oximeter (SpO$_2$), and supplemented by a single measurement of SaO$_2$ taken from blood. These conditions reflect the amount of data normally available in intensive care and are realistic when considering clinical application of INVENT. SpO$_2$ and SaO$_2$ were given different values of error (SD$_{SpO_2}$ = 1 %, SD$_{SaO_2}$ = 0.5 %) in the least squares fitting algorithm to reflect the different measurement precision.

The resulting model parameters were used to calculate the INVENT FiO$_2$ advice (FiO$_{2\,sugg}$) and to simulate the resulting SaO$_2$ (SaO$_{2\,true}$) using the INVENT suggested FiO$_2$ level.

Values of INVENT suggestions FiO$_{2\,sugg}$ and SaO$_{2\,true}$ were then compared with those set and measured clinically (FiO$_{2\,clin}$, SaO$_{2\,true}$).

In the experiments performed here, in contrast to clinical practice, values of SaO$_2$ were measured in arterial blood at each FiO$_2$ level. By fitting the model to these arterial SaO$_2$ values it was possible to calculate the optimal model description of the patient’s pulmonary gas exchange status. The resulting model parameters from this fit allowed obtaining information as to the ‘true’ variation in SaO$_2$ on changing FiO$_2$ and therefore simulate the ‘true’ resulting SaO$_2$ for the INVENT FiO$_2$ advice, i.e. SaO$_{2\,true}$. Values of SaO$_{2\,true}$ were then compared against those obtained in clinical practice (SaO$_{2\,true}$).

Differences in INVENT calculated SaO$_2$ values and clinical values were skewed and therefore all comparisons were performed graphically using scatter plots and statistically using Wilcoxon matched pairs test (Bland, 2000).

A Bland-Altman plot (Bland and Altman, 1986) was applied to assess the agreement between values of SaO$_2$ measured using pulse oximetry and arterial blood gas analysis.

3. RESULTS

Fig. 2 and table 1 compare clinical values of FiO$_2$ and SaO$_2$ (FiO$_{2\,clin}$, SaO$_{2\,true}$), with those suggested by INVENT (FiO$_{2\,sugg}$, SaO$_{2\,sugg}$). The range of values of FiO$_2$ and SaO$_2$ suggested by INVENT are narrower than those used in clinical practice. INVENT suggested values of FiO$_2$ significantly different from clinical practice ($p < 0.01$), with INVENT limiting FiO$_2$ to values lower than 64 %, which is in contrast to clinical practice where 6 patients were ventilated with FiO$_2$ levels between 65 % and 83 %. SaO$_2$ suggested by INVENT were significantly different from clinical values ($p < 0.01$) but remained above 90 % for both clinical practice and INVENT advice in all patient cases.

Fig. 3 and table 1 compare clinical values of FiO$_2$ and SaO$_2$ (FiO$_{2\,clin}$, SaO$_{2\,true}$), with INVENT suggested FiO$_2$ and the ‘true’ SaO$_2$ (FiO$_{2\,sugg}$, SaO$_{2\,true}$). The range of SaO$_{2\,true}$ is wider than that of SaO$_{2\,sugg}$ as shown in fig. 2, and values of these were significantly different ($p < 0.05$). Values of SaO$_{2\,true}$ are however within clinically acceptable limits, i.e. SaO$_{2\,true}$ remains above 90 % in all patient cases except one where SaO$_{2\,true}$ is 89 %.
4. DISCUSSION

This study has retrospectively evaluated the advice on FiO\textsubscript{2} selection provided by INVENT for intensive care patients. FiO\textsubscript{2} values and corresponding arterial oxygenation measured as part of routine clinical practice has been compared with the FiO\textsubscript{2} suggested and SaO\textsubscript{2} calculated using INVENT. It has been shown that INVENT has potential to reduce FiO\textsubscript{2} in these patients, whilst maintaining an arterial oxygen saturation at or above 90\%, thus limiting the potentially harmful effects of hyperoxia.

INVENT advice has been calculated using an oxygen transport model. The model has been identified using a clinically applicable parameter estimation method. Application of INVENT in clinical practice therefore requires no extra measurements of arterial blood, and only a small procedure varying inspired oxygen fraction which takes approximately 10-15 min (Rees et al., 2002) and may be computer controlled (Murley et al., 2005).

The oxygenation results for INVENT advice using the ‘true’ model fits ((x) in Fig. 3), are significantly different (p < 0.05) to those obtained using the clinically realistic model fit ((x) in Fig. 2). The range of SaO\textsubscript{2} values is broader, however, all SaO\textsubscript{2} remain higher than 89 \%. These are above the 88\% suggested as being within a clinically acceptable range for patients with ALI and acute respiratory distress syndrome (The Acute Respiratory Distress Syndrome (ARDS) Network, 2000). All INVENT FiO\textsubscript{2} remained below 60 \% except one (at 64 \%). 60 \% has been reported as the FiO\textsubscript{2} limit beyond which oxygen toxicity effects and absorption atelectasis may occur (Nash et al., 1967, Dantzker et al., 1975, Edmark et al., 2003). In comparison, in clinical practise 6 of these patients received FiO\textsubscript{2} in the range 60-85 \%. According to the INVENT simulation results, these patients could have been given safe levels of FiO\textsubscript{2} whilst maintaining an acceptable oxygenation.

The SD of the difference between SaO\textsubscript{2} and SpO\textsubscript{2} of 1.96 \% (see Fig. 4) is comparable to an earlier study in intensive care patients (Van de Louw et al., 2001) reporting a SD of 2.1 \%. However, Van de Louw et al. reported a mean bias of -0.02 \%, which is significantly lower than 1 \% as found in this study. This bias means that the result of the ‘true’ model fit shows a higher median SaO\textsubscript{2} than SaO\textsubscript{2,\textsubscript{sugg}}, as shown in Table 1. The specific case of a SaO\textsubscript{2} of 89 \% for the ‘true’ model fit (see Fig. 3) is an example of the worst case of SaO\textsubscript{2} and SpO\textsubscript{2} difference, where SpO\textsubscript{2} is higher than SaO\textsubscript{2}. Despite these quite large discrepancies the values of SaO\textsubscript{2,\textsubscript{true}} remains above 88\%, illustrating that the advice provided by INVENT is robust.

The penalty functions used in INVENT are based on a single intensive care physician’s preferences. The penalty functions may not comply with the preferences of all clinicians or all disease types encountered in the intensive care unit. The functions, however, could serve as a tool for reaching consensus on setting FiO\textsubscript{2}.

This study has been performed retrospectively on existing data. The SaO\textsubscript{2} resulting from INVENT advice has therefore been simulated. As such the results reported here may only serve as an indication of the applicability of the INVENT system in intensive care patients. To further evaluate the system it is necessary to perform a prospective study evaluating the use of INVENT in an intensive care unit.

Setting FiO\textsubscript{2} may per se not be regarded as the most complex problem in ventilator management. However, the results of this study indicate the feasibility of using a DSS based on physiological models combined with utility theory to provide advice in ventilator management.

### Table 1. Median and range of clinical and INVENT values.

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
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<tbody>
<tr>
<td>FiO\textsubscript{2,\textsubscript{clin}} (%)</td>
<td>53.3</td>
<td>38.6</td>
<td>82.6</td>
</tr>
<tr>
<td>FiO\textsubscript{2,\textsubscript{sugg}} (%)</td>
<td>44.0</td>
<td>33.0</td>
<td>63.5</td>
</tr>
<tr>
<td>SaO\textsubscript{2,\textsubscript{clin}} (%)</td>
<td>96.8</td>
<td>90.9</td>
<td>99.1</td>
</tr>
<tr>
<td>SaO\textsubscript{2,\textsubscript{sugg}} (%)</td>
<td>94.2</td>
<td>91.4</td>
<td>96.3</td>
</tr>
<tr>
<td>SaO\textsubscript{2,\textsubscript{true}} (%)</td>
<td>94.9</td>
<td>89.2</td>
<td>97.1</td>
</tr>
</tbody>
</table>

Median and range (Min. and Max.) of: FiO\textsubscript{2,\textsubscript{clin}}, FiO\textsubscript{2,\textsubscript{sugg}}, SaO\textsubscript{2,\textsubscript{clin}}, SaO\textsubscript{2,\textsubscript{sugg}} and SaO\textsubscript{2,\textsubscript{true}}.
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REFERENCES


