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ORIGINAL ARTICLE

Retrospective evaluation of a decision support system for controlled mechanical ventilation

Dan S. Karbing · Charlotte Allerød · Lars P. Thomsen · Kurt Espersen · Per Thorgaard · Steen Andreassen · Søren Kjærgaard · Stephen E. Rees

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Abstract Management of mechanical ventilation in intensive care patients is complicated by conflicting clinical goals. Decision support systems (DSS) may support clinicians in finding the correct balance. The objective of this study was to evaluate a computerized model-based DSS for its advice on inspired oxygen fraction, tidal volume and respiratory frequency. The DSS was retrospectively evaluated in 16 intensive care patient cases, with physiological models fitted to the retrospective data and then used to simulate patient response to changes in therapy. Sensitivity of the DSS's advice to variations in cardiac output (CO) was evaluated. Compared to the baseline ventilator settings set as part of routine clinical care, the system suggested lower tidal volumes and inspired oxygen fraction, but higher frequency, with all suggestions and the model simulated outcome comparing well with the respiratory goals of the Acute Respiratory Distress Syndrome Network from 2000. Changes in advice with CO variation of about 20% were negligible except in cases of high oxygen consumption. Results suggest that the DSS provides clinically relevant and rational advice on therapy in agreement with current 'best practice', and that the advice is robust to variation in CO.

Keywords Clinical decision support systems · Physiological models · Pulmonary gas exchange · Artificial respiration · Intensive care

D. S. Karbing (✉) · C. Allerød · L. P. Thomsen · S. Andreassen · S. E. Rees
Center for Model-based Medical Decision Support, Department of Health Science and Technology, Aalborg University, Fredrik Bajers Vej 7, E4, 9220 Aalborg East, Denmark
e-mail: dank@hst.aau.dk

C. Allerød · P. Thorgaard · S. Kjærgaard
Anaesthesia and Intensive Care, Region North Jutland, Aalborg Hospital, Aarhus University, 9000 Aalborg, Denmark

K. Espersen
Department of Intensive Care, Rigshospitalet, University of Copenhagen, 2100 Copenhagen East, Denmark

1 Introduction

Ventilator management can be considered as finding the right compromise between conflicting goals. It is necessary to provide sufficient ventilator support to prevent hypoxaemia and maintain metabolic balance, whilst preventing ventilator-induced lung injury. Finding a correct balance is important as inappropriate ventilator settings may increase mortality [26].

Computerized decision support systems (DSS) have been built to support ventilator management. The majority of these systems have been rule-based, or knowledge-based implementing heuristics of clinicians [6, 7, 15], as reviewed recently [25]. Such systems may support clinicians in finding appropriate settings, but they do not assist in understanding the individual patient's status. In contrast, few DSS have been developed utilizing physiological models [22–24, 28]. When tuned to describe an individual patient, physiological models may provide a deeper understanding of the patient's status and predict patient response to changes in therapy.

The end-goal of developing a DSS must be application and validation at the bed-side. Before prospective evaluation, it is important that a DSS is properly evaluated retrospectively. This article presents retrospective evaluation of the computerized model-based DSS for controlled mechanical ventilation originally presented by Rees et al.

[22]. The DSS has previously been successfully evaluated retrospectively and prospectively for the relatively simple problem of managing inspired oxygen (FiO_2) in intensive care patients [12, 13], and retrospectively for managing FiO_2, tidal volume (Vt) and respiratory frequency (*f*) in cardiac surgery patients [1]. In this article, the system is retrospectively evaluated for advice on FiO_2, Vt and *f* in intensive care patients with severe respiratory failure. DSS advice and resulting model simulated levels of oxygenation, acid–base balance and risk of ventilator-induced lung injury are evaluated by comparison with goals defined by the Acute Respiratory Distress Syndrome Network (ARDSNet) in 2000, which can be considered current 'best practice' [26]. It is also important that advice provided be robust to measurement error or missing values. Since, measurement of cardiac output (CO) can be associated with significant measurement uncertainty [4, 18], an analysis is carried out evaluating the sensitivity of DSS model parameters and advice to changes in CO.

2 Methods

2.1 The DSS

The DSS is presented briefly here, for more detail see the study by Rees et al. [22]. The system includes physiological models of oxygen and carbon dioxide gas exchange and storage, and a linear model of lung mechanics [3, 14, 20]. The model of pulmonary gas exchange and storage is different from that used in previous evaluations, having been modified as detailed previously [14] to provide an improved description of severe gas exchange problems. In these models, gas exchange problems are described as pulmonary shunt (fs), and ventilation/perfusion (V/Q) mismatch. V/Q mismatch is described by two parameters ΔPO_2 and ΔPCO_2. ΔPO_2 is the drop in oxygen pressure from ventilated alveoli to pulmonary capillary blood before mixing with shunted venous blood. As such, ΔPO_2 describes the oxygen gas transport problem arising due to low V/Q regions. ΔPO_2 can therefore be understood as the extra oxygen pressure required at the mouth to counter oxygenation problems due to V/Q mismatch, i.e. a ΔPO_2 of 10 kPa means air plus $\sim$10% inspired O_2 ($FiO_2 = 31\%$) is required. Similarly, ΔPCO_2 describes the increase in carbon dioxide pressure from ventilated alveoli to capillary blood hence describing the carbon dioxide gas transport problem arising due to high V/Q regions. $\Delta PCO_2 > 0$ kPa signifies insufficient removal of CO_2, and potential need for increasing minute ventilation.

To provide advice on appropriate ventilation the system requires physiological models to simulate effects of changing ventilation strategy, and also a quantification of how 'good' or 'bad' are results of these changes. Such quantification separates knowledge of physiology from preference towards outcomes. These subjective preferences can be mathematically formulated using decision theory [22], and the DSS applies this theory using penalty functions, which allocate penalty scores to increasing risk for adverse effects. The penalty functions describe risk of hypoxaemia due to arterial and mixed venous oxygen saturation (SaO_2 and SvO_2); risk of acidosis/alkalosis due to mixed venous pH (pHv); risk of oxygen toxic effects and absorption atelectasis due to FiO_2; and risk of mechanical trauma due to peak inspiratory pressure (PIP) and respiratory frequency (*f*) [1, 22]. A modification has been made to the functions presented by Rees et al. [22], altering the penalty for risk of mechanical trauma to include positive end-expiratory pressure (PEEP). The mechanical trauma penalty has two components: penalty due to high PIP alone, barotrauma, and penalty due to the combination of high frequency and pressure, volutrauma. The frequency-dependent part is such that penalty increases due to the difference between PIP and PEEP, i.e. the pressure excursion which occurs with tidal breathing. The new mechanical trauma penalty curve is illustrated in Fig. 1.

The DSS is used as follows. First, the system is tuned to the individual patient by fitting physiological models to clinical measurements. The system can then be used to simulate different ventilation strategies, and automatically provide advice as to the strategy minimizing risks of

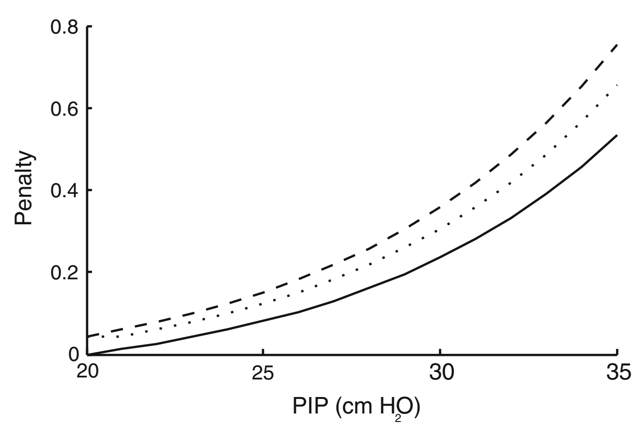

Fig. 1 Mechanical trauma penalty as function of PIP, respiratory frequency (*f*) and PEEP. PIP is the main determinant, with penalties increasing for *f* higher than 15 breaths/min as a function of *f* and the size of the pressure excursion above PEEP. The curve for PEEP = 5 cm H_2O and $f = 15$ b/min (*solid line*) shows penalty increasing with PIP. When *f* is increased to 20 b/min and PEEP maintained at 5 cm H_2O (*dashed line*) penalty is increased at all levels of PIP. When *f* is maintained at 20 b/min but PEEP is increased to 10 cm H_2O (*dotted line*) the penalty at a given level of PIP is smaller in comparison to the penalty at same *f* but lower PEEP as the pressure excursion during a breath is smaller at a higher PEEP

adverse events. The following sections present this process in more detail.

To fit the models to clinical measurements, it is necessary to consider a standard set of required clinical measurements. These are as follows. Blood is described by a single arterial blood sample drawn at the clinical FiO_2 level, i.e. the FiO_2 level selected by the attending clinician, and analyzed to obtain oxygenation (SaO_2, PaO_2), acid–base (pHa, $PaCO_2$), and haemoglobins (Hb, FHbMet and FHbCO). Metabolism (VO_2 and VCO_2) is described from measurement of inspiratory and expiratory O_2 and CO_2 levels as previously described [14]. Pulmonary gas exchange is described in two ways: anatomical dead space measured from volumetric capnography; and pulmonary shunt, ΔPO_2 and ΔPCO_2 identified by fitting the gas exchange model to O_2 and CO_2 measurements obtained from a procedure of varying FiO_2 in steps and measuring ventilation, metabolism and oxygenation status at each step [21]. This procedure allows separation of the effects of pulmonary shunt and V/Q mismatch on gas exchange [11]. The procedure is non-invasive, takes $\sim$10–15 min and is readily automated [21], such that in principle it requires no extra clinical resources. Lung mechanics is described from dynamic compliance calculated from PIP, PEEP and Vt. Body temperature is assumed to be 37°C. CO is not assumed to be part of the standard set of clinical measurements, but can be calculated from cardiac index and body surface area (BSA) using a cardiac index of 3.7 l/min/m^2, as previously reported in intensive care patients [9]. BSA can be calculated from height and weight as by Gehan and George [10]. All values except blood gas measurements can be automatically acquired by the DSS from medical measurement devices.

Models are fitted to this standard set of clinical measurements to minimize the difference between model-simulated values and clinical measurements. The difference between these values provides a quantitative measure of the quality of the model fit. The models can then be used to perform simulations of the effects of changes in FiO_2, *f* and Vt on PIP, expired gases and blood gas and acid–base status.

The DSS advice is then found by numerical optimization using a nested implementation of Brent's method [19]. The optimization method searches through different combinations of FiO_2, *f* and Vt, with each combination resulting in model simulated patient response and corresponding penalties which are summed to give a total penalty for that combination. The DSS advice is then the ventilator settings incurring minimum total penalty.

2.2 Patient data

The study was carried out retrospectively using previously published data collected from nine mechanically ventilated intensive care patients [12]. Ethical approval was obtained from the local ethical committee, and informed written and oral consent had been obtained from patients or nearest relatives. Patient data from the study were included for retrospective analysis if patients had been ventilated in controlled mechanical ventilation. The patient data included the standard set of clinical measurements outlined previously, with ventilator settings selected as part of routine clinical care constituting the baseline for calculating DSS suggestions. Currently, the system provides advice on FiO_2, *f* and Vt. In 7 of the 9 patients, the outlined standard set of clinical measurements had been performed twice within the same day at different PEEP levels. To explore the change in DSS advice with changes in PEEP, these additional measurements were included in the retrospective analysis, giving a total of 16 patient cases for the retrospective evaluation.

Of the 9 included patients, 2 were female. Mean age was 64 $\pm$ 9 years (mean $\pm$ SD). For the 16 patient cases mean PaO_2/FiO_2 was 21.4 $\pm$ 4.6 kPa, at mean FiO_2 levels of 51 $\pm$ 10%, and mean SaO_2 of 96.6 $\pm$ 2.5%. All patients had disorders in pulmonary gas exchange either due to primary infectious involvement or secondary pulmonary involvement as a consequence of severe sepsis or septic shock. All patients had lung damage as described by low values of respiratory compliance, large shunt fractions, V/Q mismatch leading to an average of 6% extra FiO_2 needed to counter oxygenation problems, and an insufficient washout of CO_2 (Table 1).

2.3 Retrospective evaluation

In each patient case, the previously defined standard set of measurements was collected, and the physiological models tuned to individual patient cases. The quality of model fit to patient data was evaluated by comparing model simulated values with measurement data. Average and spread were calculated for the baseline constituting clinically selected settings [FiO_2, Vt, f, Vt per kg predicted body weight

Table 1 Physiological model parameters

Parameter	$n = 16$
Shunt (%)	25.0 $\pm$ 10.6
ΔPO_2 (kPa)	6.11 (4.98–9.74) [1.53–20.05]
ΔPCO_2 (kPa)	1.78 $\pm$ 0.95
Vd (ml)	130 $\pm$ 24
Compliance (ml/cm H_2O)	27 (25–33) [20–62]
Hb (mmol/l)	6.27 $\pm$ 0.52
VO_2 (ml/min)	326 $\pm$ 62
VCO_2 (ml/min)	311 $\pm$ 62
CO (l/min)	8.0 $\pm$ 1.1

Summarised as mean $\pm$ SD or median (IQR) [range]

(PBW), and PEEP] and measured outcome [SaO_2, PaO_2, pHa, $PaCO_2$ and PIP], for DSS suggested settings (FiO_2, Vt, f and Vt per kg PBW) and model-simulated outcome (SaO_2, PaO_2, pHa, $PaCO_2$ and PIP), and for differences in settings and outcome between the baseline values and DSS advice. These values were then evaluated in comparison with goals defined by the ARDSNet [26] in terms of rationality, clinical relevance and soundness of suggested levels. PBW was calculated from height and gender as by the ARDSNet [26]. For the 7 patients evaluated at 2 PEEP levels, the effects of changing PEEP on DSS advice were explored.

2.4 CO sensitivity analysis

The sensitivity of the DSS's physiological models to variation in CO was analysed by fitting the models to patient data using five different CO values in each patient case. The initial CO was estimated from BSA and cardiac index of 3.7 l min^{-1} m^{-2}. The other four CO levels were the initial CO + 1 l/min, +2 l/min, −1 l/min and −2 l/min, with the ±2 l/min representing a variation of 20% in patients with a CO of 10 l/min. As such, the CO variation in the sensitivity analysis was similar to or larger than the expected precision of ±20% with thermodilution methods [4]. The DSS advice was then calculated at each CO level.

2.5 Statistics

Summary statistics are reported as mean ± SD for normally distributed values and otherwise as median (IQR) [range]. Paired t tests or Wilcoxon's signed rank tests were performed as appropriate to evaluate differences between model simulated and measured values. Median and normalized interquartile range (NIQR = 0.7413*IQR) were calculated to estimate mean and SD for comparison with published normally distributed values. Boxplots were used to assess sensitivity of model parameters and DSS advice to changes in CO. Statistical analysis was performed using SPSS (SPSS 19.0, SPSS Inc.). Figures were produced using MATLAB (MATLAB 7.11.0, The MathWorks Inc.).

3 Results

3.1 Retrospective evaluation of the DSS

In general, the mathematical models described patient data well, with absolute and relative differences between measured values and model fitted simulations being small (Table 2). For $FetO_2$ and PaO_2 differences were significant, but had no consequence on DSS advice (not shown). In the four cases where difference in measured and simulated PaO_2 was ≥1 kPa, PaO_2 was greater than 10 kPa, indicating clinically safe levels of oxygenation.

Table 2 Differences between model simulated and measured values

Value	Sim − meas	(Sim − meas)/meas
PIP	0.0 (0.0–0.0) [−1.0 to 1.0] cm H_2O	0.0 (0.0–0.0) [−3.9 to 2.9] %
$FetCO_2$	0.0 ± 0.2%	1.3 ± 4.5%
$FetO_2$	0.2 ± 0.4%*	0.6 ± 1.0%*
SaO_2	0.0 ± 0.6%	0.0 ± 0.6%
$PaCO_2$	0.0 ± 0.2 kPa	0.6 ± 3.1%
PaO_2	0.2 (−0.1 to 1.0) [−0.4 to 2.8] kPa*	2.4 (−0.9 to 8.1) [−3.5 to 22.8] %*
pHa	0.00 ± 0.01	−0.0 ± 0.2%

Summarised as mean ± SD or median (IQR) [range]

* $P < 0.05$

Figure 2 shows the DSS's advice and resulting model simulated outcomes. Figure 2a shows the DSS's FiO_2 advice and resulting simulated SaO_2 levels. The figure illustrates that the DSS uses oxygen rationally, giving high FiO_2 levels only in patients with oxygenation problems. Figure 2b shows the DSS's advice for minute ventilation and resulting simulated pHa levels, illustrating that the system only considers high levels of minute ventilation in situations of acidosis. Figure 2c shows the DSS's advice for Vt and resulting simulated PIP levels. Once again the system behaves rationally, only suggesting high Vt in situations of low PIP.

To evaluate whether the DSS's advice is rational, clinically relevant and sound in terms of the suggested levels, the clinically selected baseline values, DSS advice with corresponding model simulated outcomes and differences between the clinical baseline and DSS advice are evaluated in comparison with goals defined by the ARDSNet [26]. The ARDSNet oxygenation goals are to maintain patients within PaO_2 55–80 mmHg (7.3–10.7 kPa) and SpO_2 (i.e. SaO_2) 88–95%. As shown in Table 3, clinical baseline SaO_2 and PaO_2 were high in comparison to these ranges with average values near or above the maximum of ARDSNet oxygenation goals. In general, the DSS suggested lowering FiO_2 resulting in the majority of DSS calculated values of PaO_2 and SaO_2 being within ARDSNet limits, with all DSS SaO_2 levels being greater than 88%. When delivering ventilator volume, it is clear that the goal is to minimize tidal volume whilst holding pH and respiratory frequency within an acceptable range. This is reflected by an ARDSNet goal of 6 ml/kg for Vt per kg PBW with a maximum of 8 ml/kg, pH within the range 7.30–7.45, and a maximal f of 35 min^{-1}. The clinical baseline Vt is high compared to the ARDSNet goal with average Vt per kg PBW being 7.9 ml/kg. The clinical

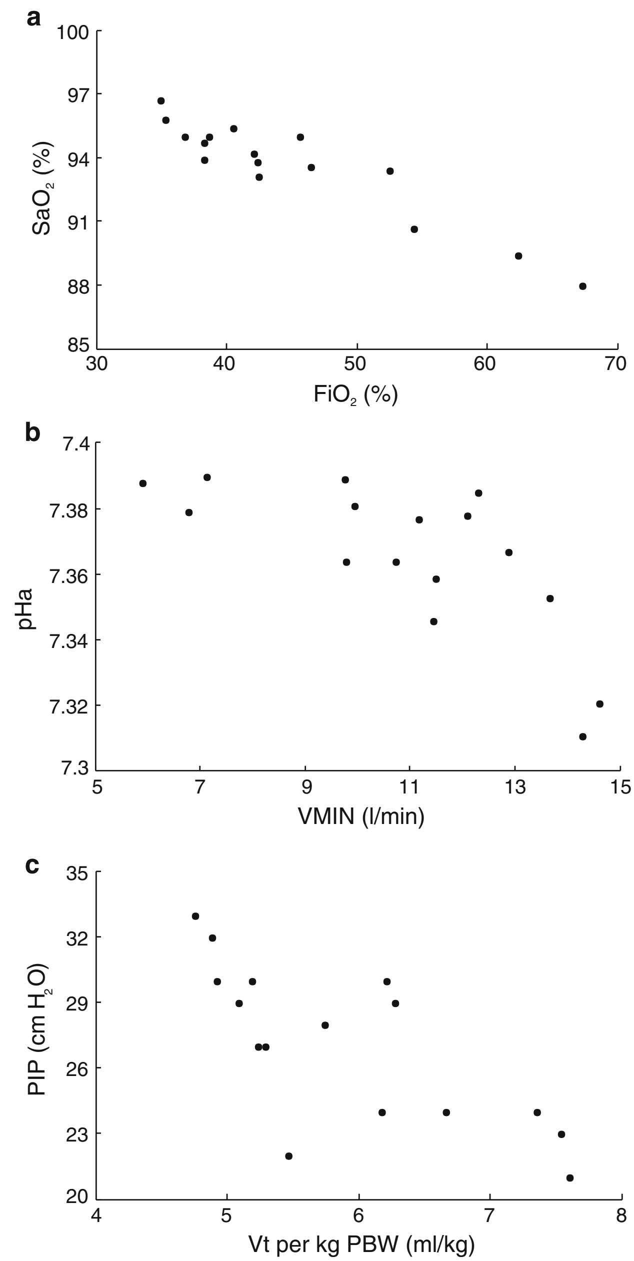

Fig. 2 Scatterplots showing DSS-suggested settings and resulting simulated respiratory variables for: **a** inspired oxygen fraction versus arterial oxygen saturation; **b** minute volume versus arterial pH; **c** tidal volume per kg PBW versus PIP

baseline pHa compared well with ARDSNet goals with the average ±1 SD being within the range of ARDSNet pH goals. The DSS suggested lower Vt per kg PBW with an average value of 5.9 ml/kg and no values above 8 ml/kg, comparing well with the ARDSNet goals. Instead of high Vt, the system in general suggested higher *f* securing that all pHa remained within ARDSNet goals. A single DSS advice on *f* was outside ARDSNet limits, at 36 min^{-1}. Whilst not directly comparable, clinical baseline and DSS PIP both indicate compliance with the ARDSNet goal of plateau pressure ≤30 cm H_2O.

Table 3 DSS advice, model-simulated outcome and changes from baseline-measured values

Value	Baseline[a]	DSS advice[b]	DSS–baseline[c]
FiO_2 (%)	58.9 ± 16.3	42.2 (9.5) [34.9–67.3]	−14.0 ± 12.9
Vt (ml)	566 ± 102	425 ± 89	−141 ± 76
Vt per kg PBW (ml/kg)	7.9 ± 1.3	5.9 ± 1.0	−2.0 ± 1.1
f (min^{-1})	19 ± 4	26 ± 6	7 ± 5
PEEP (cm H_2O)	12.4 ± 3.9	12.4 ± 3.9	–
SaO_2 (%)	95.8 ± 3.1	94.1 (1.3) [88.0–96.7]	−2.2 ± 1.7
PaO_2 (kPa)	10.4 ± 2.6	8.6 (1.0) [7.0–12.3]	−1.7 ± 0.0
pHa	7.39 ± 0.06	7.37 (0.02) [7.31–7.39]	−0.03 ± 0.05
$PaCO_2$ (kPa)	5.9 ± 0.7	6.3 ± 0.8	0.4 ± 0.8
PIP (cm H_2O)	32 ± 5	27 ± 4	−5 ± 3

Summarised as mean ± SD or median (NIQR) [range]

[a] Clinically selected baseline settings and measured values of SaO_2, PaO_2, pHa, $PaCO_2$ and PIP

[b] DSS suggested FiO_2, Vt and *f*; clinically selected baseline level of PEEP; model simulated SaO_2, PaO_2, pHa, $PaCO_2$ and PIP resulting from DSS advice

[c] Difference between DSS-suggested settings and model-simulated outcome and the measured clinically selected baseline settings and SaO_2, PaO_2, pHa, $PaCO_2$ and PIP

Table 4 shows the effects of different PEEP levels on the DSS's advice. PEEP was changed in 7 of the 9 patients. In all but 1 patient (pt7) a PEEP increase led to a reduction in pulmonary shunt. This improvement in gas exchange resulted in the DSS suggesting reductions in FiO_2 ranging from 0.4 to 12.0%. In the remaining patient, an increase in shunt resulted in the DSS advising on an increase of 5% in FiO_2. In two patients (2, 4) respiratory compliance increased on increasing PEEP, with it decreasing in three (3, 5, 7) and effectively remaining the same in two (6, 8). In the two patients where compliance increased the DSS recommended increasing Vt which resulted in improving pH. In the three patients with worsening compliance the DSS suggested reducing Vt, increasing *f* and accepted a lower pH level. Changes in Vt per kg PBW ranged from 0 to 2.5 ml/kg. Despite these changes in therapy, all of the DSS suggestions resulted in model simulated patient response adhering to the respiratory goals of the ARDSNet study, as illustrated in Table 3, except in one case where *f* was 1 min^{-1} too high.

Table 4 DSS advice upon changes in PEEP

Pt	PEEP cm H_2O	Compl. ml/cm H_2O	Shunt %	FiO_2%	Vt ml/kg	f min^{-1}	SaO_2%	pHa	PIP cm H_2O
2	10	23	20.9	42.0	5.7	28.0	94.2	7.359	28
	15	31	13.6	35.3	6.3	28.7	95.8	7.367	29
3	10	33	28.9	52.5	6.2	20.8	93.4	7.389	24
	15	26	17.3	40.5	5.2	27.2	95.4	7.364	30
4	7	35	17.7	38.6	7.5	21.7	95.0	7.385	23
	5	27	20.0	38.2	6.7	22.3	94.7	7.377	24
5	12	62	22.5	46.4	7.6	17.4	93.6	7.381	21
	17	31	17.7	45.6	5.1	25.6	95.0	7.364	29
6	10	25	28.4	42.3	5.5	18.9	93.8	7.388	22
	15	25	20.4	36.7	5.2	22.7	95.0	7.379	27
7	10	40	36.6	62.3	7.3	21.9	89.4	7.378	24
	20	27	50.0	67.3	4.8	32	88.0	7.346	33
8	9	20	40.0	54.3	4.9	34.5	90.7	7.311	30
	14	23	32.1	42.4	4.9	35.5	93.1	7.321	32

PEEP, clinically selected level of PEEP; Compl., Measured dynamic respiratory compliance; Shunt, Model fitted shunt parameter; FiO_2, Vt per kg PBW and f DSS advice; SaO_2, pHa and PIP, Model simulated values resulting from DSS advice

The system therefore behaved rationally in responding to changes in PEEP level.

3.2 CO sensitivity

Figure 3 illustrates boxplots of changes in model parameters and DSS suggestions on FiO_2 with changes in CO. Shunt (fs) changes with CO, but the magnitude is small with average changes of 2% shunt per 1 l/min change in CO. Changes in other model parameters and DSS FiO_2 suggestions were negligible, except for a few patient cases showing relatively large changes in either ΔPO_2 or FiO_2. In these patients, VO_2 values were large, necessitating an equally large oxygen delivery to prevent hypoxaemia. Changes in Vt and f were also negligible with ranges of changes within −4 to 10 ml and 0 to 1 min^{-1}, respectively.

4 Discussion

The presented results indicate that a DSS based upon physiological models can provide reasonable advice in the management of intensive care patients with severe respiratory abnormalities. The physiological models fitted measured data well, providing a consistent physiological picture of individual patient cases. The advice suggested was reasonable both qualitatively and quantitatively. Qualitatively, the DSS only advised on high levels of FiO_2, minute ventilation and tidal volume in patients with oxygenation problems, acidosis and low PIP, respectively. Quantitatively, suggested settings of Vt and f, and calculated levels of oxygenation and pH were all in line with the ARDSNet respiratory goals from 2000 [26], in contrast to baseline settings and outcome values which had been selected and measured as part of routine clinical care. The results indicate that the system has the potential to evaluate and manage patients as individuals, whilst remaining within clinical recommendations, and that the system's suggestions are clinically relevant. This is consistent with previous evaluations of the DSS indicating both standardization and individualization of ventilator management [1, 12, 13]. Compared to the cardiac surgery patients included in the study by Allerød et al. [1], the patients included in this study on average had 10% higher shunt, 3 kPa higher ΔPO_2 and compliance was 15 ml/cm H_2O lower, and as such represent a patient group where it is more difficult to find the optimal compromise between securing gas exchange and preventing ventilator-induced lung injury.

In addition to testing the system with updated penalty functions, a new mathematical model of gas exchange and in a more complex clinical setting, this evaluation has shown that the system can provide reasonable advice when the measurement of CO is inaccurate. Of parameters describing pulmonary gas exchange, only shunt changed notably with CO, but the magnitude of this change was small. The DSS's advice was insensitive to CO in almost all situations, except that of elevated metabolism and suspected poor circulation. In this case, it can be argued that there is a clinical need for accurate measurement of CO. For the sensitivity analysis, CO was estimated from BSA and a cardiac index of 3.7 l/min/m^2. Whilst this may not reflect true CO, it is sufficient for a simulation study of CO sensitivity, and as the results show, inaccuracy in CO estimation has little bearing on resulting model parameters or DSS suggestions. It is important to note that the CO sensitivity analysis did not include physiological alterations in shunt as seen with therapeutic or experimental changes in CO [5, 8]. These changes would be handled appropriately by the DSS by re-tuning models to the individual patient and calculating new advice.

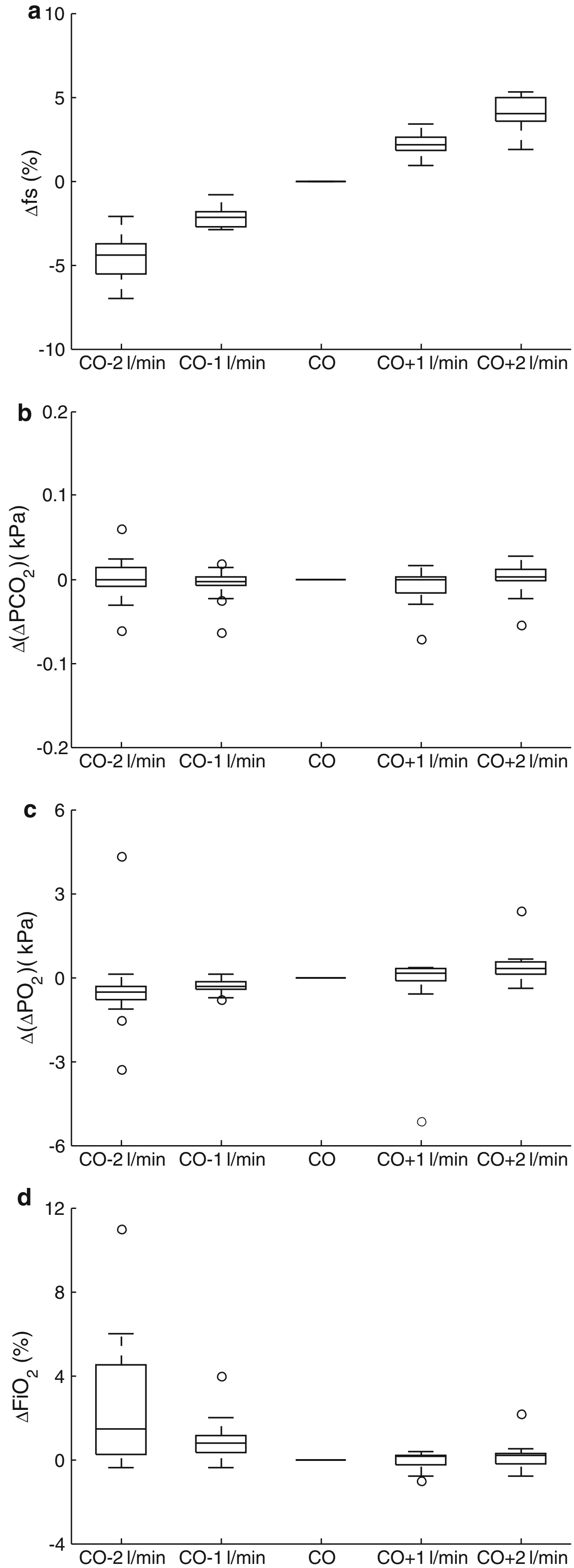

Fig. 3 Boxplots of changes in model parameters and DSS suggestions on FiO_2 with changes in CO from baseline (baseline CO = BSA*3.7 l/min/m^2). Boxes represent the 25th to 75th percentile of data, *horizontal line* in *boxes* represent the median, *dashed lines* with *whiskers* represent range of data excluding outliers. Outliers are data points more than 1.5 times the interquartile range away from the box. Outliers are illustrated individually by *circles*. **a** Changes in shunt gas exchange model parameter (Δfs). **b** Changes in ΔPCO_2 gas exchange model parameter ($\Delta(\Delta PCO_2)$). **c** Changes in ΔPO_2 gas exchange model parameter ($\Delta(\Delta PO_2)$). **d** Changes in DSS suggestions on inspired oxygen fraction (ΔFiO_2)

The major limitation of this study is its retrospective nature with recommended advice not applied to patients. The system's advice assumes that changes in FiO_2, Vt or *f* will not modify the underlying physiological picture of the patient, in engineering terms—that model parameters are constant on performing simulations. There are, of course situations where this is not true. Large perturbations in tidal volume may recruit or over distend lung units changing gas exchange or lung mechanics. The DSS's advice should therefore be considered as 'target' values, with the system taking small steps towards these targets, and re-tuning the physiological models after each step. In this way, a strategy can be defined for the patient, and this strategy modified according to changes due to ventilator adjustment.

The ARDSNet study from 2000 as well as subsequent studies by the ARDSNet and others includes goals for SpO_2, PaO_2 and pHa, with the latter two requiring arterial blood sampling (e.g. [16, 17, 26, 27]). Titrating ventilator settings to reach these goals may require several arterial blood samples, which may be too demanding in resources for intensive care units with high patient:nurse ratios. Similarly, the DSS requires a single arterial blood sample analysis for suggesting therapy, which may be necessary several times a day in a patient changing lung status.

The penalty functions used to calculate DSS advice are by nature subjective, and may not comply with preferences of all clinicians or disease types encountered in the intensive care unit. This, we do not regard as a limitation. The separation of well-established knowledge on physiology, as included in the models, from functions describing subjective clinical preference towards outcome, enables preferences to be discussed alone and in quantitative terms [2]. The process of deriving functions which, for example, explicitly require consideration of how much acidosis one would trade off for reduction in inspiratory pressure can be a productive way to evaluate consensus between clinicians. Despite the subjectivity of the current penalty functions, it is reassuring that results presented here suggest that they provide advice on FiO_2, *f* and Vt which are both rational and in line with ARDSNet goals.

The current version of the system does not provide advice on PEEP and *I*:*E* ratio, and correct setting of PEEP remains an elusive clinical problem [16, 17] and part of the development strategy for the system. Nevertheless, the system appears to respond appropriately to clinical PEEP changes, both in terms of its quantification of the effects on lung function, and in the advice provided on changes in FiO_2, Vt and f, to accommodate changes in gas exchange, lung recruitment or over-distension on modifying PEEP maintaining model simulated SaO_2, pHa and PIP within ARDSNet goals. The model-simulated results indicate that two types of patients in particular, could benefit from the DSS suggestions following PEEP changes. In patients where an increase in PEEP led to worsening compliance the DSS suggested reducing Vt per kg PBW by up to 2.5 ml/kg reducing risk of ventilator-induced lung injury. In patients where PEEP increase reduced shunt, the DSS suggested reductions in FiO_2 of up to 12.0% reducing the risk of oxygen toxic effects.

In this article, a model-based DSS has been retrospectively evaluated for its advice on inspired oxygen fraction, tidal volume and respiratory frequency in intensive care patients. The DSS advice has been shown to be in agreement with the respiratory goals of the ARDSNet from 2000, which can be considered the current 'best practice'. In addition, results indicate that both the gas exchange model of the DSS and the DSS advice were robust to variations in CO.

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