A Decision Support System for Mechanical Ventilation

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Description and Retrospective Clinical Evaluation

PhD Thesis by

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River Publishers
Aalborg

ISBN 978-87-92982-32-2 (e-book)

Published, sold and distributed by:
River Publishers
P.O. Box 1657
Algade 42
9000 Aalborg
Denmark

Tel.: +45369953197
www.riverpublishers.com

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A Decision Support System for Mechanical Ventilation: Description and Retrospective Clinical Evaluation

Introduction: In intensive care, identification of appropriate ventilator settings can be a difficult balancing procedure. This can, however, be seen as important as inappropriate ventilator settings have been shown to increase patient mortality. To aid in the process of identifying appropriate ventilator settings decision support systems have been developed. This thesis has addressed the feasibility and retrospective evaluation of a decision support system based on physiological models and penalty functions in a decision theoretic approach. This system can provide advice for ventilator settings in intensive care patients from routinely available clinical data.

Methods: The decision support system INVENT is presented including a description of the mathematical models included in the system, these being the physiological models of gas-exchange and lung mechanics, and the model of clinical preference including penalty functions. Retrospective evaluation of the system is described in stable post-operative CABG-patients, and, after inclusion of a more complex model of gas-exchange, in critically ill ALI and ARDS patients. In addition, the model of clinical preference has been evaluated comparing this to clinical opinion.

Results: This thesis shows that INVENT can describe the physiological status of both stable post-operative patients and critically ill ALI and ARDS patients. INVENT has been shown to provide reasonable advice for fraction of inspired oxygen, respiratory frequency and tidal volume, in these patients. Evaluation of the model of clinical preference has illustrated an apparent lack of consensus towards ventilator settings between clinical experts. Despite this, application of the penalty functions in INVENT has provided advice consistent with the ARDSNet recommendations for mechanical ventilation, i.e. good clinical practice.

Conclusion: A model based decision support system for mechanical ventilation, INVENT, has been presented and retrospectively evaluated. INVENT has been shown to provide reasonable advice for both stable patients and critically ill patients in-line with ARDSNet recommendations.

List of Papers

The thesis is based upon the following articles:

I. Rees, SE, Allerød C, Murley, D, Zhao Y, Smith BW, Kjærgaard S, Thorgaard P, Andreassen S. Using physiological models and decision theory for selecting appropriate ventilator settings. Journal of Clinical Monitoring and Computing 2006; 35: 421-429.

II. Allerød C, Rees SE, Rasmussen BS, Karbing DS, Kjærgaard S, Thorgaard P, Andreassen S. A Decision Support System for suggesting ventilator settings: Retrospective evaluation in cardiac surgery patients ventilated in the ICU. Computer Methods and Programs in Biomedicine 2008; 92:205-212

III. Karbing DS, Allerød C, Thomsen LP, Espersen K, Thorgaard P, Andreassen S, Kjærgaard S, Rees SE. Retrospective evaluation of a decision support system for controlled mechanical ventilation. Med Biol Eng Comput 2012 50:43-51

IV. Allerød C, Karbing DS, Thorgaard P, Andreassen S, Kjærgaard S, Rees SE. Variability of preference towards mechanical ventilator settings: a model based behavioural analysis. Journal of Critical Care 2011; 637.e5-637.e12

Content

Abbreviation

ALI	Acute Lung Injury
ARDS	Adult Respiratory Distress Syndrome
ASV	Adaptive Support Ventilation
BMI	body mass index (kg/m^2)
BSA	body surface area
CABG	coronary artery bypass grafting
CO	cardiac output
COHb	carboxy haemoglobin
Cdyn	dynamic complianc
CaO_2	arterial oxygen content
$CmvO_2$	mixed venous oxygen content
DPG	2,3 diphosphoglycerate
DSS	Decision Support System
f	respiratory frequency
f2	fraction of perfusion to compartment labelled 2
fA2	fraction of ventilation to alveolar compartment labelled 2 of non- shunted blood
$FetCO_2$	fraction of end expired carbon dioxide
$FetO_2$	fraction of inspired oxygen
FiO_2	fraction of inspired oxygen
Fs	fraction of shunt
Hb	haemoglobin
ICU	intensive care unit
I:E ratio	inspiratory expiratory ratio
MetHb	methaemoglobin
MODS	multi-organ failure score
MV	minute ventilation
ODC	oxygen dissociation curve
PAC	pulmonary artery catheter
PBW	predicted body weight
$PaCO_2$	arterial carbon dioxide partial pressure
PaO_2	arterial oxygen partial pressure

PEEP	positive end-expiratory pressure
ΔPCO_2	difference of carbon dioxide pressure from ventilated alveoli to lung capillary blood
pHa	arterial pH
pHv	mixed venous pH
PIP	peak inspiratory pressure
$PaCO_2$	arterial carbon dioxide pressure
$PmCO_2$	model predicted carbon dioxide pressure
PvO_2	venous oxygen pressure
$PvCO_2$	venous carbon dioxide pressure
ΔPO_2	difference in oxygen pressure from alveolar air to lung capillary blood
PRVC	Pressure regulated volume control
RQ	respiratory quotient
Qs/Qt	fraction of shunt
SaO_2	arterial oxygen saturation
SmO2	model predicted arterial oxygen saturation
SpO_2	oxygen saturation measured by pulse oximeter
SvO_2	mixed venous oxygen saturation
VA	alveolar ventilation
VCO_2	production of carbon dioxide
VO_2	oxygen consumption
Vmin	minute ventilation
V_D	anatomical dead space
Vt	tidal volume

Chapter 1

1.1 Introduction

The majority of critically ill patients residing in the Intensive Care Unit (ICU) suffer from respiratory failure and require mechanical ventilation to support sufficient oxygen delivery and carbon dioxide (CO_2) removal. In patients with ICU stay longer than 24 hours, 80 % require mechanical ventilation [1] and 13 % suffer from Acute Lung Injury (ALI) or Acute Respiratory Distress Syndrome (ARDS). In these patient groups mortality is high, ranging from 32 % in ALI to 60 % in ARDS [1-4], with some indication that this may be decreasing [5].

During more than a decade it has become evident and accepted that mechanical ventilation contributes to aggravation of, or even induces, ALI [6-9], and potentially contributes to the pathogenesis of multi organ failure [7]. Randomised trials have shown that inappropriate ventilator settings can increase risk of patient mortality [10-11]. The importance of selecting appropriate ventilator settings is therefore clear, where appropriate settings can be seen as those achieving the goal of sufficient oxygen delivery and CO_2 removal, whilst minimising the risk of ventilator induced lung injury.

This balance can be difficult to accomplish as, for example, increasing tidal volume (Vt) both improves oxygenation and carbon dioxide removal but simultaneously increases peak inspiratory pressure (PIP) and thereby the risk of volu/barotrauma. Identification of the ventilator settings which provides a suitable balance is a complex procedure requiring: continuously updated and implemented knowledge as to the impact of ventilator settings on patient outcome; understanding of the individual patient's patophysiological status through interpretation of the patient's data; and assumptions as to how different ventilator settings will influence the patient status. This difficulty is reflected in clinical practice, for example, the benefit of lung protective ventilation using low tidal volume strategy is well documented [11], but the proportion of patients ventilated using low tidal volume remains relatively low [12-13]. This

difficulty may not be surprising as the interpretation of substantial amounts of data is a task for which humans have limited ability [14].

Different approaches to supporting the clinician in the process of setting the ventilator have been developed, these ranging from paper based clinical guidelines or protocols to computerised decision support systems.

Clinical guidelines for mechanical ventilation have been presented [11, 15-16]. Application of the most well known, that of the ARDSNET, has in a randomised trial been shown to significantly reduce patient mortality, by reduction of tidal volume and maintenance of plateau pressure below 30 cmH_2O [11]. Despite the benefit in clinical studies, the broad impact is not convincing. The surviving Sepsis Campaign implements as an element of the bundles a recommendation of maintaining a plateau pressure of less than 30 cmH_2O for mechanical ventilated patients [17]. As recently, reported by Levy et al. compliance with the entire bundle has increased and the adjusted hospital mortality decreased [18]. However, compliance with the bundle elements increased significantly except for the element of maintaining a plateau pressure below 30 cmH_2O. Other recent studies illustrates that average tidal volumes remain higher than recommended i.e. 8.4 ml/kg versus 6 ml/kg predicted body weight [19,20]. These results indicate that adherence to guidelines for lung-protective mechanical ventilation is insufficient. The reasons for the lack of routine use of clinical guidelines in general, and specifically in relation to lung protective ventilation, have been evaluated in several studies [21-25]. Cabana et al. have proposed a framework for analysing the reasons for non-adherence to guidelines and grouped these into three different areas [21]. One group describes “Knowledge”, which includes lack of awareness and lack of familiarity. A second group describes “Attitude”, which includes lack of agreement with guidelines in general or with the specific guideline, lack of motivation/inertia of previous practice, lack of self-efficacy and lack of outcome expectancy. The third group describes “Behaviour”, including external barriers such as environmental factors, guideline factors and patient factors. Using this framework Rubenfeld and al. have performed a survey to identify different barriers towards lung-protective ventilation [24]. This survey identify

no lack of awareness, however, as the study was conducted in hospitals which had participated in the ARDSNet low tidal volume trial, this might not be expected to be representative. For attitude, lack of agreement with guidelines in general, i.e. guidelines seen as a challenge to autonomy, was reported, as was lack of agreement with specific guidelines. In particular, concerns were expressed as to appropriate use of low tidal volume as this may cause tackypnea, hypercapnia, acidosis, worsening of oxygenation, and patient discomfort. In addition, lack of recognition that the patient was suffering from ALI/ARDS was reported. These barriers to use of low tidal volume ventilation were confirmed by Dennison et al. in a later study, with these authors also identifying a lack of knowledge [25]. Solutions to overcome the barriers in relation to adherence to guidelines have been suggested and include both improving technical skills e.g. through education, and non-technical skills, which might include clinical decision support [22-27].

In addition to paper guidelines, several computer systems have been presented since the 1980s [28-41]. These systems apply various approaches, the majority being rule-based systems implementing clinical guidelines and as such automating the heuristics reasoning of the clinician, usually as rules [28-40]. Other systems implement physiological models, aiming at providing an understanding of the patient state and making explicit the many compromises which exist when setting the ventilator [32]. The following section will provide an overview of the development and a status of the different systems.

The majority of the Decision Support Systems (DSS) published, including those applied in clinical practice, implement rules. One of the most prominent of these over the last 20-30 years is a collection of computer-based protocols known as the Salt Lake City protocols or HELP system. As part of this, East et al. have presented an open loop rule-based system supporting the clinician in the process of mechanical ventilation and weaning of ARDS patients [29-33]. The system supported both assist and controlled ventilation and could provide advice for Vt, positive end expiratory pressure (PEEP), fraction of inspired oxygen (FiO_2), respiratory frequency (f) and inspiratory to expiratory (I:E) ratio. The system has been evaluated in a multi-center randomised controlled

trial to determine the efficacy of protocolised mechanical ventilation using computerised decision support in comparison with a control group ventilated non-protocolised. As the maximal multi-organ failure score (MODS) and maximal barotrauma score were significantly lower for the protocol group, it was concluded that the efficacy was best for the computerised decision support [32-33]. This research team continues to publish on the development and application of computer protocols [27, 42-44].

In 1992, Dojat et al presented a rule-based closed loop DSS [34-36] controlling Pressure Support weaning. The DSS automatically regulates pressure support ventilation (PSV) to the lowest level, which maintains respiratory frequency, Vt and end-tidal CO_2 pressure within ranges which have been predefined to describe acceptable ventilation [34]. The system has been evaluated in clinical randomised controlled trials comparing to physician-controlled weaning [35-37] showing significant reduction in mechanical ventilation duration in 2 trials [35-36], and no difference in one [37]. The system is commercially available under the name SmartCare®.

In 2002, Brunner et Iotti presented a closed loop rule based system Adaptive Support Ventilation (ASV), which can provide both controlled and assisted ventilation automatically switching between these modes [38]. The system regulates ventilation such that a minute volume set by the clinician is delivered aiming at a calculated target Vt, adjusting f according to measured lung mechanics at each breath. The system has been evaluated in a prospective multicenter study including 48 patients. Compared to conventional ventilation the system was at least as safe and effective [38]. The system is commercial available under the name Intelligent Ventilation®.

Several systems are currently under development but have not entered routine clinical practice [39-40]. Kwok et al. have presented an adaptive neuro fuzzy inference system (ANFIS) deriving rules from expert clinical opinion for advising on FiO_2 [39]. ANFIS was evaluated in a study including 71 scenarios from 3 mechanically ventilated patients and 9 clinicians working regularly in the ICU [39]. It was concluded that compared to other fuzzy logic systems

ANFIS correlated better to clinical opinion and the advice provided was interpretable.

Tehrani et al. have presented the system FLEX [40], an advisory tool for ventilator settings and an automatic weaning controller. FLEX functions in both closed and open loop control, in a variety of ventilator modes, using both rules and some physiological models [40]. FLEX provides advice for maximal and optimal respiratory frequency, required minute volume (MV), I:E ratio adjustment, FiO_2, PEEP, Vt, and a check for weaning conditions. The open loop advisory system has been retrospectively evaluated in a preliminary study including 10 patients [40]. In this study, it was concluded that, when comparing to clinicians selection of ventilator settings, FLEX demonstrated potentially better patient management [40].

These rule-based systems may provide appropriate patient adaptive advice on ventilator settings, but do not aid the clinician in obtaining a deeper understanding of the patient's state, or enable the clinician to perform simulations of how different ventilator settings might affect the patient. An alternative approach to decision support has been proposed, based on physiological models and decision theory [41]. The physiological models can be tuned to the individual patient and in combination with utility functions, in a classical decision theoretic approach [45], and provide patient specific advice taking into consideration the unavoidable compromises in the process of selecting ventilator settings.

In 1993, Rutledge et al. presented the DSS VentPlan, based on physiological models and decision theory [41]. The DSS was an open loop system providing advice on FiO_2, PEEP, Vt and respiratory frequency. VentPlan required information regarding patient diagnosis to be input into a belief network to create probability distribution for unmeasured patient parameters. These, in combination with measured patient parameters, enabled estimation of patient specific physiological parameters. The system could then simulate the effect of various ventilator settings and, by combining to the plan-evaluator including utility functions based on decision theory, recommend ventilator settings. The

system's capability of predicting the effect of ventilator changes was evaluated retrospectively in cardiac surgery patients [41]. VentPlan is no longer under development and no prospective clinical evaluation has been performed. However, an approach using physiological models and decision theory can be seen as having advantages over that of computerised rules for the following reasons:

- Mathematical models can be tuned to the individual patient, via parameter estimation, enabling system advice to be patient specific.
- Model simulations allow 'what if' questions to be answered, providing information of how advice possible will affect the patient.
- The approach enables separation of physiological knowledge from clinical preference, the latter potentially being locally or culturally specific. This separation allows preferences to be modified to local situations without re-design of physiological models.

Despite these apparent advantages, building such systems is expensive. Mathematical models need to be formulated which have the correct abstraction to describe the individual patient when tuned to routinely available clinical data. In addition, the physiological model parameters describing the patient should have clinical meaning, aiding the clinician in the process of understanding the patient. The physiological models should be applicable for a range of mechanically ventilated patients, for example from simple to manage post-operative patients to those with ALI or ARDS. In addition, utility functions are required which represent clinical opinion and different types of patients.

1.2 Aim of the PhD project

In the Center for Model-Based Medical Decision Support (MMDS) at Aalborg University a decision support system INVENT based upon physiological models and a model of clinical preference in a decision theoretic approach is under development, the goal of this system being to advise in the process of mechanical ventilation. Developing such a system includes research activities related to mathematical modelling and clinical retrospective and prospective

evaluation. The primary goal of this thesis is to retrospectively evaluate the feasibility of the advice provided by the system for three ventilator settings (fraction of inspired oxygen (FiO_2), tidal volume (Vt) and respiratory frequency (f)) for controlled ventilation and the preference functions included in the system.

This primary goal has been addressed as follows:
To set the scene for the evaluation of the DSS, the structure and function of the system is presented in Chapter 2. This work is based upon publication I [46]

The thesis describes the evaluation of the feasibility of the DSS INVENT's advice in a homogeneous, well-monitored patient group, ventilated using a controlled mode and generally considered uncomplicated to ventilate. INVENT's advice on f, Vt and FiO_2 has retrospectively is evaluated in twenty uncomplicated post-operative coronary artery bypass graphing (CABG) patients, comparing the systems advice to the settings selected by the residing clinician. This work is based upon publication II [47]

The thesis describes the evaluation of feasibility of the DSS INVENT's advice in a severely ill group of ICU patients suffering from ALI or ARDS considered difficult to ventilate. INVENT's advice has retrospectively been evaluated in 16 patient cases, comparing the system's advice to the settings selected by the residing clinician and to the ARDSNet guidelines for mechanical ventilation [11]. In addition, as the aim is to develop a DSS, which is robust to measurement error or missing values, an analysis of the sensitivity of the DSS physiological model parameters and the advice to variation in cardiac output (CO) has been performed. This work is based upon publication III [48]

This thesis describes the evaluation of whether the model of clinical preference is an adequate representation of clinical opinion. In the evaluation the physiological models included in INVENT used to generate standardised model-simulated patient cases representing a range of patients mechanically ventilated in the ICU. The use of the physiological models enabled comparison of the clinicians preferred combination of FiO_2, Vt and f in the same patient

cases, thereby separating true difference in clinical opinion from variability in patient cases. In addition, the clinicians' opinion on each other's advice and the advice provided by the DSS were evaluated. This work is based upon publication IV [49]

Chapter 2 Description of the DSS and Methods

This Chapter describes the DSS "INVENT". In addition, the chapter presents the strategy and methods for evaluation of INVENT's advice and the preference functions included in INVENT.

2.1 The DSS INVENT

The DSS is based upon physiological models and a model of clinical preference in a decision theoretic approach. This section will describe the structure of the DSS; the physiological models and the model of clinical preference; and the steps included in the use of the DSS.

2.1.1 The structure of the DSS INVENT

The structure of DSS is illustrated in Figure 1 [46]. The DSS includes physiological models of oxygen and carbon dioxide transport and storage and of lung mechanics simulating the effect of various combinations of ventilator settings. Also included is a model of clinical preference towards the goals of sufficient oxygenation and carbon dioxide removal and the risk of ventilator induced lung injury, based on mathematical functions in a decision theoretic approach [45].

The physiological models include parameters describing lung function, metabolism, circulation and blood status**.** These parameters may aid in the process of understanding the patient's physiological status, and may be assumed to remain relatively constant for model simulations. For example, when describing gas exchange abnormalities, pulmonary shunt and ventilation perfusion (V/Q) mismatch might be seen as preferable parameters compared to arterial oxygen pressure (PaO_2) or arterial carbon dioxide pressure ($PaCO_2$), as these latter two do not provide any physiological interpretation of the reason behind compromised gas exchange. In addition, PaO_2 will not remain constant upon changes in inspired oxygen fraction but rather respond immediately, and both PaO_2 and $PaCO_2$ will respond to changes in alveolar ventilation. Parameter values are either measured directly or estimated through the models by including known values of patient specific ventilator settings and physiological

model variables, all these being listed in the legend of Figure 1. Estimated patient specific parameter values provide a picture of the patient's state and enable simulations of the effect of change in ventilator settings.

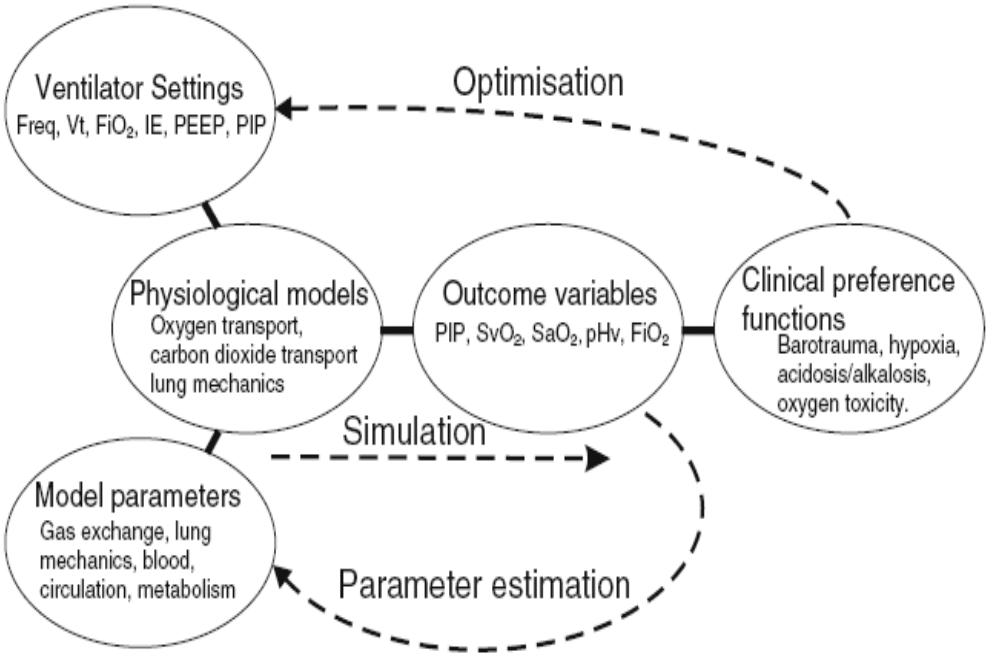

Figure 1. Illustrates the structure of the decision support system INVENT. Ovals represent components of INVENT which includes ventilator settings (FiO_2, f Vt, I:E ratio, PEEP and PIP); physiological model parameters (shunt, fA_2, f_2, Vd, dynamic compliance, DPG, Hb, COHb, metHb, temp, CO, VO_2 and VCO_2); physiological models and their variables ($FetCO_2$, $FetO_2$, SaO_2, PaO_2, $PaCO_2$, pHa, SvO_2, PvO_2, $PvCO_2$ and pHv); surrogate outcomes (PIP, SvO_2, SaO_2, pHv and FiO_2); and the functions included in the model of clinical preference (Barotrauma, hypoxaemia, acidosis/alkalosis, oxygen toxicity). Reproduced with kind permission from Springer + Business Media: Rees et al. ([46], p.423) Fig. 1.

The model of clinical preference includes mathematical functions defined as penalty functions to express the potential detrimental effect of various combinations of ventilator settings. The process of defining the penalty functions will be described later, however, functions have been defined for risk of low oxygenation; oxygen toxicity and absorption atelectasis; acidosis or alkalosis; and baro/volutrauma. The total risk of detrimental effect of any

combination of ventilator settings is expressed as the sum of the functions. A high total penalty indicates a high risk of detrimental effect and thereby a reduced preference for the specific combination.

The DSS INVENT can be used for:

- Estimation of patient specific parameter values as to provide a picture of the patient's physiological state
- Simulation of the effect of various combination of ventilator settings
- Optimisation defined as identification of the combination of ventilator settings, which incur minimum total penalty, a process occurring automatically through repeated simulation.

2.1.2 Models in the DSS INVENT

In the following section, the physiological models and the model of clinical preference will be described. For the physiological models, a detailed description of the mathematics will be omitted as this has been described and published previously [49-52]. For the model of clinical preference, a detailed description will be provided.

Mathematical model of oxygen and carbon dioxide transport and storage

The structure of the model of oxygen and carbon dioxide transport and storage is illustrated in figure 2 with this figure including symbols and equations describing the transport of oxygen [50-53]. The model includes five compartments, i.e. lung, arterial and venous blood including red blood cells, interstitial fluid and tissue, and parameters describing cardiac output (CO), oxygen consumption (VO_2) and carbon dioxide production (VCO_2) [51-52].

In the model, the lung is divided in two compartments, each ventilated and perfused differently. The compartments are each ventilated by a fraction of total alveolar ventilation (VA), where VA is total ventilation omitting anatomical dead space (V_D), e.g. compartment 2 is ventilated by fA2*VA. Perfusion of the compartments is described as a fraction of cardiac output (CO) excluding the fraction of venous blood shunted (Qs/Qt or fs) through the lungs without being involved in gas exchange, e.g. compartment 2 is perfused by f2*(CO- Qs/Qt).

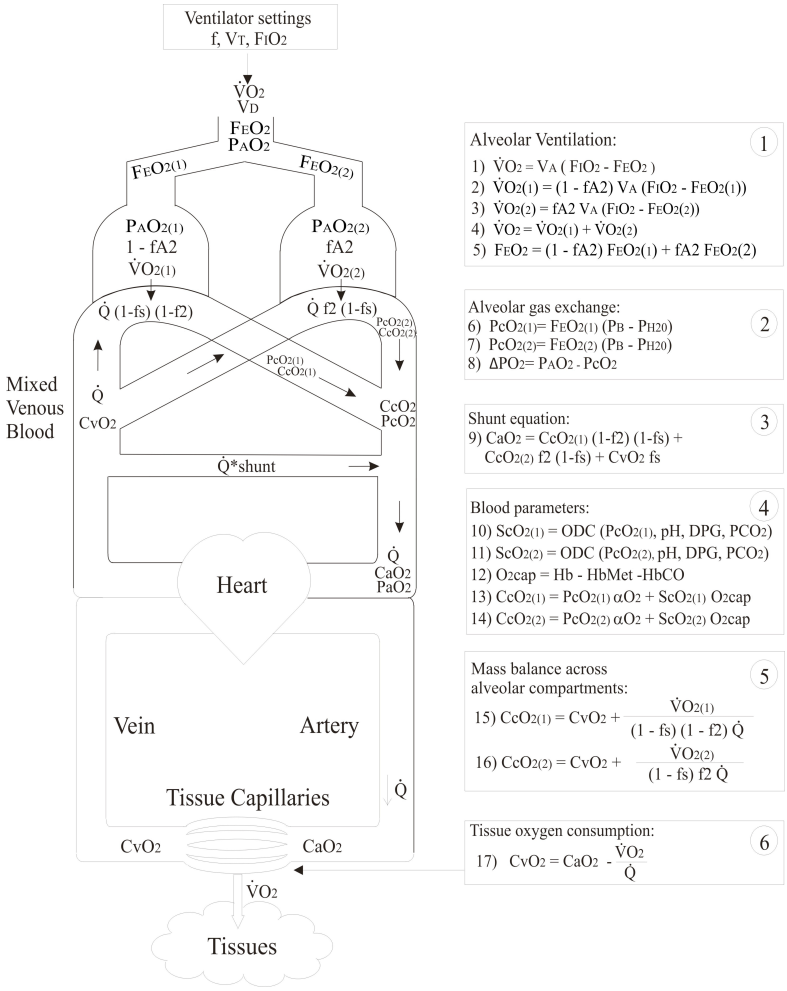

Figure 2. The structure of the physiological model describing oxygen and carbon dioxide transport to the tissues including symbols and equations describing oxygen transport. Box 1 describes alveolar ventilation. Eq. 1 describes oxygen flow into the alveoli (VO_2) as a product of alveolar ventilation (VA) and inspired oxygen fraction (FiO_2) minus expired oxygen fraction ($FetO_2$). VA is the product of tidal volume (Vt) minus dead space (VD) and respiratory frequency (f), i.e. VA = f (Vt –VD). Eq. 2 and 3 describe oxygen flow into the alveoli compartments ($VO_2(1)$, $VO_2(2)$) using the fraction of ventilation to the second alveolar compartment (fA2). Eq. 4 describes the total oxygen flow into the alveoli (VO_2) as the sum of oxygen flow into alveoli compartment 1 and 2 ($VO_2(1)$, $VO_2(2)$). Eq. 5 describes the expired oxygen fraction (FEO_2 or $FetO_2$) as a sum of fractions expired from the alveoli compartments. Box 2 describes alveolar gas exchange. Eq. 6 and 7 describe oxygen partial pressure in the lung capillary compartment 1 and 2 ($PcO_2(1)$, $PcO_2(2)$) assuming these equal to alveolar oxygen partial pressure for each compartment ($PAO_2 = FEO_2(PB – PH_2O)$). Eq. 8 describes the oxygen pressure drop (ΔPO_2) from ventilated alveoli (PAO_2) to pulmonary capillary before admixture of shunted venous blood (PcO_2). Box 3, eq. 9 describes arterial oxygen concentration (CaO_2) as a product of lung capillary blood oxygen concentration from each compartment ($CcO_2(1)$, $CcO_2(2)$) mixed with the fraction of shunted venous blood (fs). f2 represents fraction of total cardiac output (CO or Q) perfusing compartment 2. Box 4 describes calculation of variables describing blood. Eqs. 10 and 11 calculate for each compartment oxygen capillary saturation ($ScO_2(1)$, $ScO_2(2)$) implementing the oxygen dissociation curve (ODC) adjusting for pH, DPG, and PCO_2. Eq. 12 calculates haemoglobin oxygen carrying capacity (O_2cap) adjusting for abnormal haemoglobin forms (HbMet, HbCO). Eqs. 13 and 14 calculates capillary oxygen concentration for each compartment ($CcO_2(1)$, $CcO_2(2)$) as the sum of haemoglobin bound and freely dissolved oxygen. Box 5, eqs. 15 and 16 calculate for each compartment oxygen capillary concentration ($CcO_2(1)$, $CcO_2(2)$) as the sum of venous oxygen concentration (CvO_2) and the increase in oxygen concentration due to equilibration with alveoli. Box 6, eq. 17 calculates venous oxygen concentration (CvO_2) as the arterial oxygen concentration minus the tissue oxygen consumption.

This model of gas-exchange has been shown to fit the data of various patient groups [50, 54-55] and to reproduce results of the reference experimental technique for measuring gas-exchange, i.e. the MIGET technique [56-57].

In the DSS gas exchange abnormalities are represented through V_D, pulmonary shunt (Qs/Qt or fs) and values of the parameters fA2 and f2 describing V/Q mismatch [50]. As the clinical implication of the parameters fA2 and f2 are difficult to interpret, these values can be transformed by the model to the parameters ΔPO_2 and ΔPCO_2. ΔPO_2 describes an oxygen pressure drop between alveoli and end lung capillary blood. Typically normal alveolar partial pressure on breathing air is about 13 kPa and this equilibrates with blood to give similar end lung capillary and arterial values. Low V/Q areas are insufficiently ventilated with therefore insufficient oxygen to fully saturate the haemoglobin of the relatively large perfusion of these areas. As a consequence lung capillary blood partial pressure of oxygen will fall and present as a partial pressure drop (ΔPO_2) between alveoli and end lung capillary blood. If this drop is 10 kPa then the alveolar partial pressure of oxygen will need to be increased by 10 kPa to normalise the oxygenation of blood in these regions. Increasing alveolar partial pressure by 10 kPa requires increasing inspired oxygen partial pressure by 10 kPa. As barometric pressure is approximately 100 kPa this translates into an increase of FiO_2 of 10 %. In short, a ΔPO_2 of 10 kPa indicates that a FiO_2 of 0.31 (atm. Air equal to 21% plus 10%) is required to fully oxygenate haemoglobin of low V/Q regions of the lung. Similarly, ΔPCO_2 describes the increase in carbon dioxide pressure from ventilated alveoli ($FetCO_2$) to pulmonary capillary blood before admixture of shunted venous blood [54]. Clinically $\Delta PCO_2 > 0$ kPa can be interpreted as insufficient CO_2 removal and indicate need for increased minute ventilation if CO_2 retention due to V/Q mismatch should be avoided.

In the blood transport and storage of O_2 and CO_2 are represented in a set of mass balance and reaction equations describing the acid-base chemistry of the blood (figure 3) [50, 52].

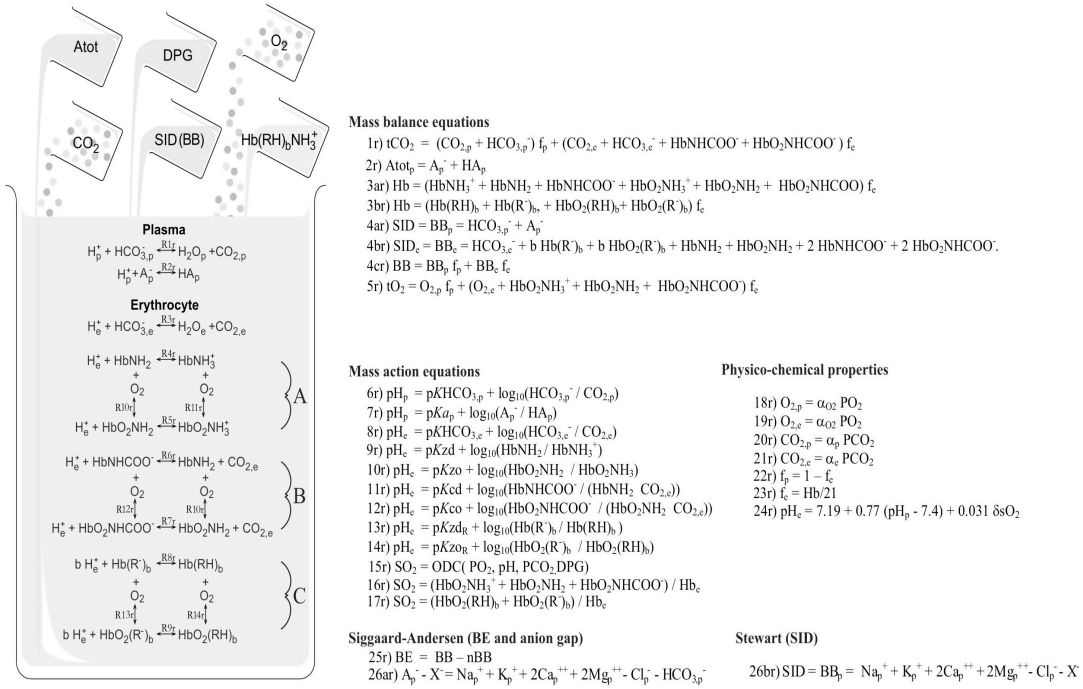

Figure 3 Mathematical model of acid-base chemistry of the blood including mass balance equations 1r-5r; mass action equations 6r-17r; equations describing physico-chemical properties of the blood 18r-24r; equation representing calculation of base excess (BE) 25r; and equations describing electrical neutrality 26ar-br.

In the interstitial fluid and tissue cells the transport and storage of O_2 and CO_2 are described by reaction equations implemented as mass balance and mass action equations (figure 4) [51]. These models of gas-exchange, oxygen transport, acid-base and CO_2 transport are included in INVENT enabling it to simulate the effect of changes in ventilator settings. It is important to note that the model does not include any representation of renal compensation of acidosis or alkalosis.

Evaluation of the mathematical models of oxygen and carbon dioxide transport and storage is not part of this thesis. They have previously been shown to be able to simulate the effect of changes in ventilation on acid-base and CO_2 levels [51-52], and to accurately simulate the effects of mixing of oxygenated and de-oxygenated blood samples similar to the mixing of shunted venous and non-shunted blood in the lung capillaries [53].

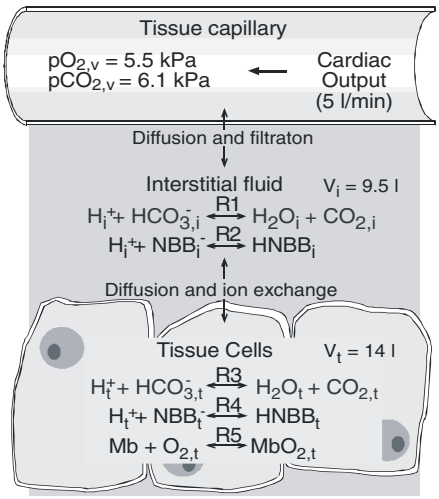

Figure 4. Reaction equations describing the acid-base chemistry of the interstitial fluid and tissue cells (muscle cell) and illustrating the CO_2 stores as either dissolved CO_2 or as bibarbonate in both compartments. The values depicted for CO, $PO_{2,v}$. $PCO_{2,v}$, interstitial volume (V_i) and intracellular volume (V_t) represents values chosen as normal for a person weighting 70 kg. (Non-bibarbonate buffer in intestitial fluid (NBB_i^-); in tissue cells (NBB_t^-), Myoblobin (Mb)). Reproduced with kind permission from Begell House, Inc

Estimation of patient specific gas-exchange parameters values of shunt (Qs/Qt or fs) and V/Q mismatch requires an experimental procedure of 10 to 15 min [50,54,58]. In the procedure, FiO_2 is varied in 4-6 different levels depicting oxygen saturation (SpO_2 or SaO_2) as a function of expired oxygen fraction ($FetO_2$) as illustrated in figure 5 and figure 6. The shape of SpO_2/SaO_2-$FetO_2$ curve is defined by the degree of pulmonary shunt and V/Q mismatch with increase in shunt values depressing the curve vertically while increase in V/Q mismatch right shifts the curve. After the small experiment sampling SpO_2/SaO_2-FiO_2 data patient specific parameter values are estimated in a fitting procedure. This procedure is performed in one of two ways with a differing degree of complexity.

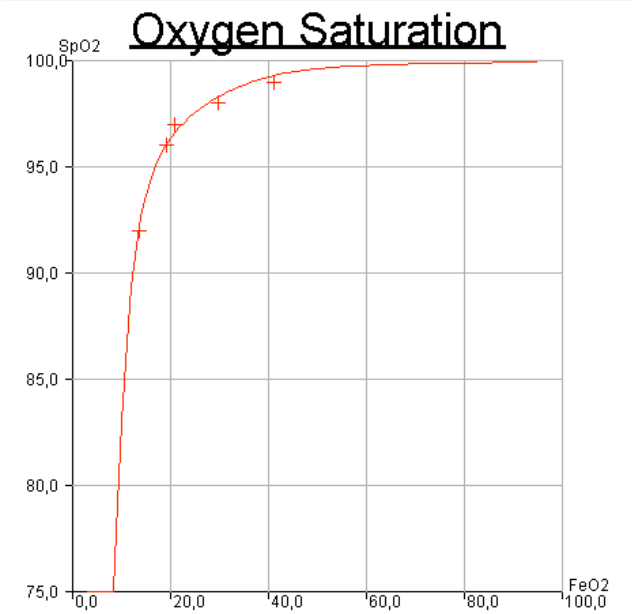

Figure 3. Example of measured SpO_2-FeO_2 data (crosses) model fitted curve (solid line) for a single post-operative CABG patient.

The first of the possible fitting procedures is that which can be considered most simple (figure 3). Parameter estimation is performed by fitting the oxygen model including the equations in figure 2 to measured values of SpO_2 and setting the fraction of non-shunted blood describing the perfusion of compartment 2 (f2) to 0.9 [49,55,57]. V/Q mismatch can then be described by the value of fractional ventilation distribution fA2 i.e. the fraction of the ventilation (fA2) to the compartment perfused by 90 % of the non-shunted pulmonary blood. A value of fA2 = 0.9 indicate 90 % of ventilation going to 90 % of perfusion, i.e. a V/Q of 1, whereas values of fA2 below 0.9 indicate V/Q mismatch, with values lower than 0.6 representing substantial V/Q mismatch and below 0.3 severe. Through repeated simulations, the combination of parameters values of Qs/Qt (fs) and fA2 resulting in the smallest weighted residual sum of squared difference (WRSS) between model simulated SaO_2 (SmO_2) and measured values of SpO_2 are identified.

$$WRSS = \sum_{i=1}^{n} \frac{(SmO_2 - SpO_2)^2}{(\sigma_{SpO_2} + \sigma_{Horiz})^2}$$

This function includes the standard deviation describing measurement error on both measurement of SpO_2 (σ_{spO2}) and $FetO_2$ (σ_{Horiz}). To ensure that these error weightings are in units of oxygen saturation, σ_{Horiz} is calculated as the difference in SmO_2 caused by increasing $FetO_2$ by the standard deviation of $FetO_2$ measurement (σ_{FetO2}). σspO_2 is set to 0.01 and σ_{FetO2} was set to 0.005 . When the parameter values of Qs/Qt (fs) and fA2 have been estimated, these are used in the model of oxygen and carbon dioxide to describe gas-exchange for both oxygen and carbon dioxide. In addition, the equations describing oxygen are used to calculate the value of ΔPO_2 to describe V/Q mismatch. Calculation of ΔPCO_2 is not possible using this simple fitting procedure.

The second of the possible fitting procedures is that which can be considered most difficult. Parameter estimation is performed by fitting to both measured SpO_2-$FetO_2$ data, a single more accurate measurement of oxygenation i.e. SaO_2 obtained from a single arterial blood gas sample [59], and measured values of $PaCO_2$ and $FetCO_2$. This requires fitting to the equations describing both oxygen and carbon dioxide transport and storage, but it is then possible to estimate three parameters describing gas-exchange, i.e. Qs/Qt (fs), $fA2/\Delta PO_2$ and $f2/\Delta PCO_2$. This has been shown to provide an improved description of measured patient data, especially in severely ill patient cases [59]. Through repeated simulations fitting to four or more SpO_2-$FetO_2$ data points, one SaO_2-$FetO_2$ data point, and one $PaCO_2$-$FetCO_2$ data point the values of parameters Qs/Qt (fs), fA2 and f2 can be found which result in the smallest weighted residual sum of squared difference (WRSS) between model simulated (m) and measured values using the following error function.

$$WRSS = \frac{4}{n}\sum_{i=1}^{n}\left(\frac{(SmO_{2i} - SpO_{2i})^2}{\sigma_{SpO_2}^{\ 2}}\right) + \frac{(SmO_2 - SaO_2)^2}{\sigma_{SaO_2}^{\ 2}} + \frac{(PmCO_2 - PaCO_2)^2}{\sigma_{PaCO_2}^{\ 2}}$$

Where n is the number of SpO_2-$FetO_2$ data sets, and SmO_2 and $PmCO_2$ are the model predicted SaO_2 and $PaCO_2$, respectively. The number of SpO_2-$FetO_2$ data sets are normalised to four data points and the standard deviations

representing measurement errors are set to $\sigma SpO_2 = 0.02$ [60], $\sigma SaO_2 = 0.005$ [61], and $\sigma PaCO_2 = 0.09$ kPa [60].

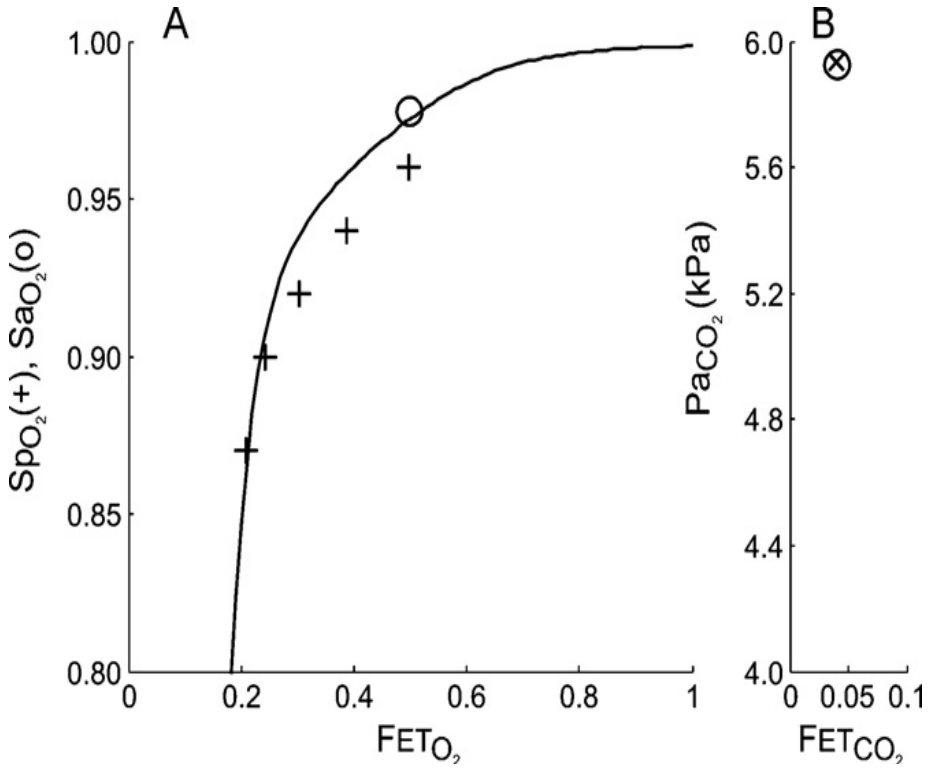

Figure 4. Example of simultaneous fitting the model to measured values SaO_2 or $SpO_2/FetO_2$ and $FetCO_2/PaCO_2$. (A) Measured end-tidal fraction of oxygen ($FETO_2$) and SpO_2 (+) or SaO_2 (O) and model fitted curve (solid line) for a single patient. (B) Measured end-tidal fraction of carbon dioxide $FETCO_2$ and $PaCO_2$ (O) and model simulated values (+).Reproduced with kind permission from Elsevier. Karbing et al. ([59] p.243) fig.2

When values of Qs/Qt (fs), fA2 and f2 have been estimated, the values of ΔPO_2 and ΔPCO_2 can be calculated. Figure 4 illustrates an example of fitting the model of oxygen and carbon dioxide transport and storage to patient data for oxygen and carbon dioxide using this more complex fitting technique.

Mathematical models of lung mechanics

In the DSS lung mechanics is described in a simple one compartmental model including one parameter (dynamic compliance (C_{dyn})) [46]. The value of dynamic compliance (ml/ cm H_2O) is calculated as the change in volume, i.e. Vt, divided by the corresponding change in pressure, PIP minus PEEP. Under

the assumption that compliance remains constant, the model can be used to simulate the effect of different Vt on PIP. This assumption will most likely be invalid for all but minor changes in Vt and will as such be addressed further in the Discussion.

Mathematical model of clinical preference

To enable quantification of preference or dislike towards the goals and side effect (outcomes) of different ventilator settings, the DSS INVENT includes mathematical functions in a decision theoretic approach [45]. These functions are in INVENT called penalty functions as these express the potential detriments and thereby the dislike towards the different outcomes. In the DSS, penalty functions have been associated with hypoxemia, oxygen toxicity and absorption atelectasis, acidosis and alkalosis and barotrauma (Figure 7). Each of these outcomes is associated with a surrogate outcome variable for which a value can be either obtained directly from the ventilator (oxygen toxicity and absorption atelectasis), or estimated through the models (the remaining three). The surrogate outcome FiO_2 represents risk of oxygen toxicity and absorption atelectasis, and venous pH represents risk of acidosis and alkalosis. The surrogate outcome for risk of hypoxemia is the sum of two functions, arterial oxygen saturation (SaO_2) expressing the risk of local ischemia, and mixed venous oxygen saturation (SvO_2) the risk of global ischemia, as it reflects both oxygen delivery and consumption. Barotrauma is represented by PIP and is scaled according to frequency, i.e. a higher frequency at the same pressure incurs a larger penalty. PIP values below 20 cmH_2O have been defined not to incur penalty, however if frequency is above 15 a small penalty is added to ensure a frequency within the normal range in situations where lung mechanics are normal.

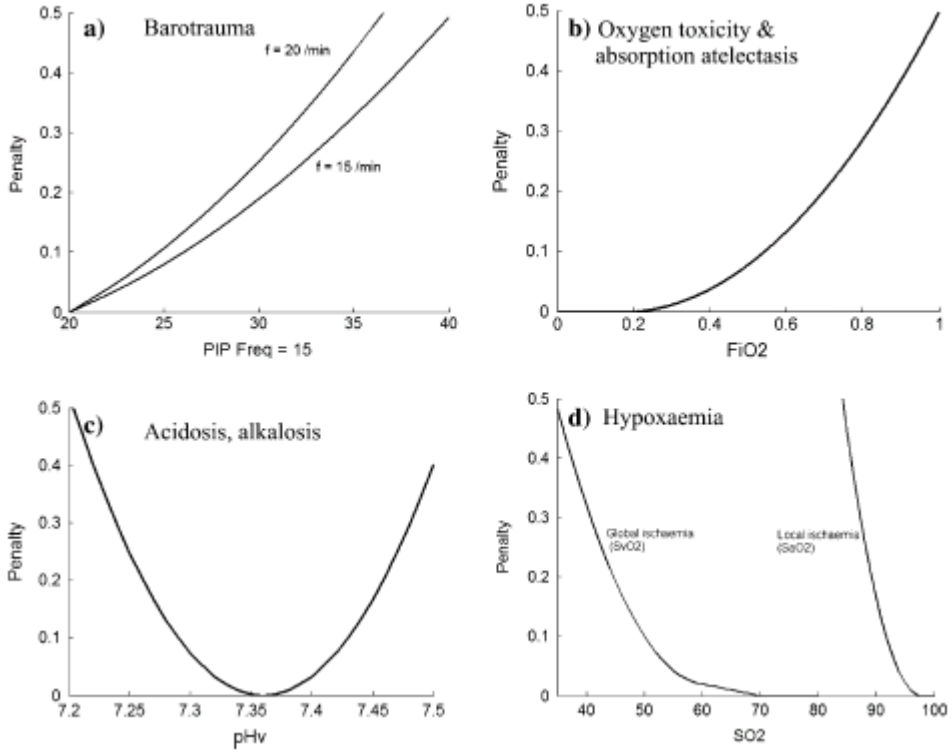

Figure 7 Penalty functions included in the DSS described in chapter 1. Barotrauma penalty is a function of PIP and respiratory frequency (a). For different respiratory frequency individual penalty curves represent incurred penalty, illustrated by two curve examples f =20 and 15 breathmin^{-1}. For all respiratory frequencies PIP below or equal to 20 incur penalty 0. In addition, for respiratory frequency above 15 a small penalty is added to the barotrauma penalty. Oxygen toxicity and absorption atelectasis penalty is a function of FiO_2 (b). FiO_2 equal to 0.21 are defined to incur penalty 0. Acidosis and alkalosis penalty is a function of mixed venous pH (c). Mixed venous pH equal to 7.36 is defined to incur penalty 0. Insufficient oxygenation (hypoxemia) penalty is represented by the sum of two functions; SvO_2 describes global ischemia, and SaO_2 local ischemia (d). SvO_2 equal to or above 70 % are defined to incur penalty 0, and SaO_2 equal to or above 98 % are defined to incur penalty 0. Reproduced with kind permission from Springer + Business Media: Rees et al. ([46], p.425) Fig. 3

The shapes of the functions represent the relationship between the potential detrimental effect of outcome values and associated penalty, and have been derived from the author's own subjective opinion in collaboration with an engineer. The functions have been scaled according to each other, such that the subjective dislike toward a particular outcome is the same on all graphs

whereby the total penalty, i.e. total risk of potential detrimental effects, can be express by adding the penalties from the four different outcomes. In the scaling process, 20 test patient cases from patients considered not difficult to ventilate, were used. For each patient case, the author suggested the values of FiO_2, f and Vt which she believed were appropriate for the patient given model simulations performed using these values. Subsequently the penalty functions were scaled according to these values and simulations. This process resulted in the penalty functions performing in a manner consistent with the author's opinion. These are named here as penalty functions version 1 or model of clinical preference version 1.

The scaling and evaluation of the model of clinical preference version 1 was performed in patient cases ventilated at low respiratory pressures and at the same PEEP level, i.e. 5 cmH_2O. This evaluation did not provide any information of behaviour of the model of clinical preference at high ventilatory pressures (high PEEP and/or PIP). To explore if the penalty functions could provide reasonable advice in severely ill patients ventilated at high pressures, the DSS was used in a few data sets from such patients. The advice generated was however, not reasonable as the DSS suggested combinations of Vt well above 6 ml/kg and even 8 ml/kg, and very high PIP levels, i.e. above 30 cmH_2O. This result was mainly due to the penalty function for risk of mechanical trauma not including PEEP but only depending on PIP and f. The penalty for risk of volu/barotrauma was altered to penalty for risk of mechanical trauma which includes two components, penalty due to PIP alone, barotrauma, and penalty due to a combination of the frequency and pressure, volutrauma. The volutrauma part is a multiplicative function of the respiratory frequency (f) and the pressure excursion between PIP and PEEP. Following implementation of this modification, the four penalty functions have been rescaled according to each other in a process including data sets from 10 severely ill patients and a collaboration between the author and an engineer. This rescaling resulted in adjustment of the mechanical penalty function such that an increased penalty is incurred for PIP values above 25 cmH_2O (figure 8). The modified model of clinical preference are named here as version 2.

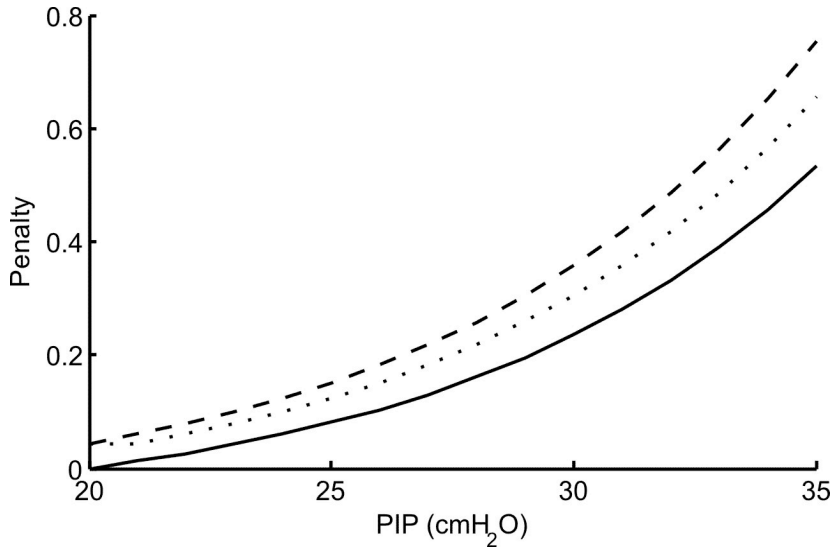

Figure 8 Mechanical trauma penalty as a function of peak inspiratory pressure (PIP), respiratory frequency (f) and positive end-expiratory pressure (PEEP). PIP is the main determinant, with penalty increasing for f higher than 15 breaths/min, as a function of f and the size of pressure excursion above PEEP. The curve for PEEP = 5 cmH_2O and f =15 breath/min (solid line) shows penalty increasing with PIP. When f is increased to 20 breath/min and PEEP maintained at 5 cmH_2O (dashed line) penalty is increased at all levels of PIP. When f is maintained at 20 breath/min but PEEP is increased to 10 cmH_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 for this higher PEEP. Reproduced with kind permission from [55] Fig. 1

2.1.3 Application of the DSS INVENT

The following section describes the three step application of the DSS to provide advice on appropriate settings of Vt, FiO_2 and f. These steps involve the fitting of the model of gas exchange as described in section 2.1.2. As two different fitting procedures are possible, a simple and more complex, this naturally results in differences within these steps. These will be referred to as "situation 1" using the simple fitting procedure and "situation 2", using the more complex fitting procedure. These two situations correspond to the strategies used for the two patient groups described in section 2.4. Situation 1 for post-operative CABG patients, and situation 2 for severely ill patients. An additional difference in the two situations presented here is that CO is only measured in

scenario 1, a point which will be discussed further in the presentation of these steps.

The three steps include:

- Step 1 data collection and estimation of patient specific parameter values for the physiological models by fitting to measured patient data.
- Step 2 evaluation of the quality of the model fit to clinically measured patient data.
- Step 3 suggestion of the combination of Vt, FiO_2 and f which balances goals and potential adverse effects of mechanical ventilation.

In addition to providing advice for Vt, FiO_2 and f, the DSS may be used by the clinician to explore the effect of different combination of Vt, FiO_2 and f.

The user interface of INVENT including data from an example of a post-operative CABG patient is illustrated in figure 9. The left hand side (LHS) displays ventilator settings, penalties and function buttons of the system. These buttons are clicked when the user wants to perform simulations of the effect of different ventilator settings or wishes the DSS to provide advice for optimal setting of Vt, FiO_2 and f. The right hand side (RHS) displays values describing end tidal gases, arterial and venous blood. In the LHS and RHS the majority of the variables, have three different columns, "Current" representing measured values, "Simulated" representing input (f, Vt, FiO_2) or outputs from model simulations, and "Optimal" representing the values calculated by the system minimising the total penalty. The bottom of the user interface presents the patient specific parameters describing gas-exchange, lung mechanics, blood, cardiac output and metabolism. These are measured, calculated or estimated, as will be described below, and are assumed to remain constant when simulating the effect of different combinations of Vt, FiO_2 and f.

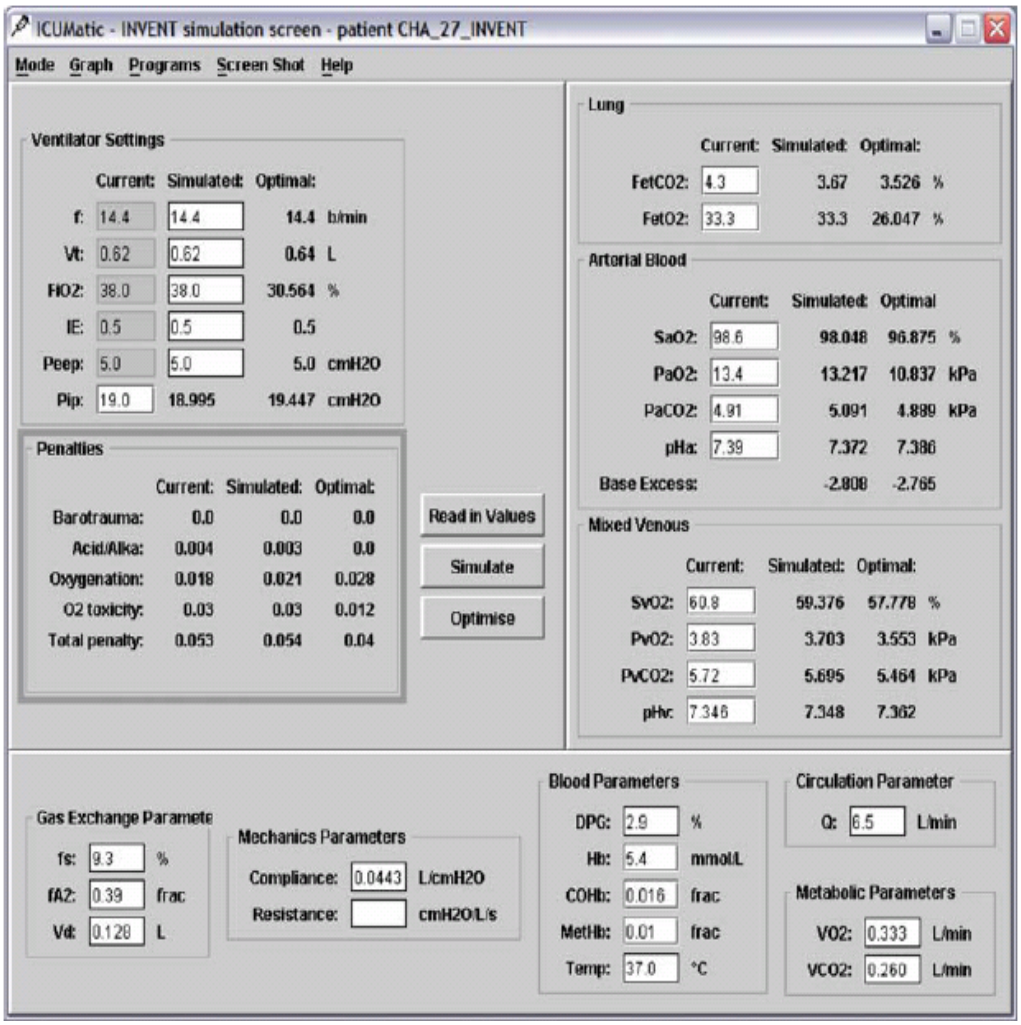

Figure 9. User interface of the DSS INVENT. The interface is subdivided into 3 sections. The left hand-side includes ventilator settings and penalties displayed as current, simulated and optimal. The right hand-side includes variables describing the lungs, arterial and venous blood also as current, simulated and optimal. The bottom of the screen displays patient specific physiological model parameters organised according to organ system. For illustration, data from a post-cardiac patient is displayed. Reproduced with kind permission from Springer + Business Media: Rees et al. ([46], p.426) Fig. 4

Step 1: Data collection, calculation and estimation of patient specific physiological model parameters

Collection of patient data is performed by connecting intensive care equipment to a standard PC running the DSS and a research data-base which automatically retrieves patient data [62]. In all situations Vt, f, PEEP, PIP, I:E ratio are retrieved from the ventilator. In "situation 1" SpO_2, FiO_2, and $FetO_2$ are retrieved from a pulse oximeter and side-stream gas analyser (Anaesthetic Gas

monitor type 1304, Brüel & Kjaer, Denmark). In "situation 2" SpO_2, FiO_2 and $FetO_2$ are measured by side-stream paramagnetic oxygen analyser (Oxigraf, Mountain View CA, USA,) while $FetCO_2$ and in addition, V_D are measured by a stand alone respiratory monitor (CO2SMO Plus, Novametrix Medical Systems, Wallingford CT, USA). In all situations, patients are monitored with an intra-arterial line from which arterial blood samples can be drawn. In "situation 1" monitoring includes a pulmonary artery catheter (PAC) (Continuous Cardiac Output, Edwards Life Science LLC, Irvine, USA) enabling measurements of CO by thermal dilution and mixed venous blood samples to be drawn. In all situations measured values from blood gas samples (ABL 525 or 725 Radiometer Medical A/S, Copenhagen, Denmark) are entered by hand into the DSS.

The patient specific parameters included in the models are as follows: pulmonary gas exchange and lung mechanics (V_D, Qs/Qt (fs), fA2/ ΔPO_2, f2/ΔPCO_2, and Cdyn), blood (2,3 diphosphoglycerate (DPG), Haemoglobin (Hb), carboxyhaemoglobin (COHb), methaemoglobin (MetHb), temperature); CO, and metabolism (VO_2 and VCO_2). To obtain values for all these parameters measured patient data are either used directly or used to calculate and estimate patient specific parameter values. This process depends to some degree on how the specific patient is monitored. In "situation 1", monitoring includes a pulmonary artery catheter (PAC) as part of routine practice, enabling measurements of CO. In "situation 2", which is similar to use of the DSS in the majority of patients mechanically ventilated in the ICU, monitoring does not include using a PAC, and a value for CO must be obtained using a different approach. The parameter calculation and estimation including the variation due difference in monitoring devices will be described below.

Blood parameters:

In "situation 1" values of Hb, COHb and MetHb are measured in mixed venous blood. In addition, mixed venous blood is used to calibrate the ODC curve and hence estimate the DPG value.

In “situation 2” the values of Hb, COHb and MetHb are obtained from the arterial blood sample. For DPG, the values are obtained in one of two different ways. If SaO_2 < 97 %, DPG is calculated by calibration of the ODC as for venous blood , otherwise it is set equal to 5 mmol as in normal fully oxygenated arterial blood [51]. With no mixed venous blood samples being available, SvO_2, PvO_2, $PvCO_2$ and pHv are estimated from the measured arterial blood gas values using the model of oxygen and carbon dioxide transport and storage [51-53].

Metabolic and circulatory parameters:

In “situation1” CO is measured using a PAC and thermal dilution technique, and VO_2 is then calculated by using the Fick equation, i.e. $VO_2 = CO(CaO_2-CmvO_2)$, with CaO_2 and $CmvO_2$ calculated as described in the legend of figure 2**.** VCO_2 is subsequently estimated to enable the best possible fit of the carbon dioxide model to measured values of arterial and venous blood gasses. Calculation of respiratory quotient (RQ), i.e. $RQ=VCO_2/VO_2$, are used to test if the estimated value of VCO_2 is clinically reasonable, i.e. RQ between 0.7 and 1.0.

In “situation 2” VO_2 and VCO_2 are calculated from measurements of inspiratory and expiratory O_2 and CO_2 using the alveolar air equation as described by Karbing et al [59]. With no PAC available CO is calculated from cardiac index (CI) and body surface area (BSA), using a value of CI of 3.7 $l/min/m^2$ as previously reported in a comparable patient group of intensive care patients [63]. BSA is calculated from patient height and weight using the equation defined by Gehan and George [64].

Gas exchange parameters:

In “situation 1” V_D is calculated using the alveolar air equation i.e. $VO_2 = (FiO_2-FeO_2)\ f\ (Vt - V_D)$, with values of f, FiO_2, $FetO_2$, Vt being measured and VO_2 calculated using the Fick equation as described above. The values describing Qs/Qt (fs) and V/Q mismatch are estimated as described in section 2.1.2, for the simple fitting procedure.

In "situation 2" V_D is measured by volumetric capnography (CO2SMO Plus, Novametrix Medical Systems, Wallingford CT, USA). The values describing Qs/Qt (fs) and V/Q mismatch ($fA2/\Delta PO_2$ and $f2/\Delta PCO_2$) are estimated as described in section 2.1.2, for the more complex fitting procedure.

Lung mechanics parameters:
In all situations, Cdyn is calculated by dividing the measured value of Vt by the measured pressure change, i.e. PIP minus PEEP.

Step 2: Quality of the model fit

Following data collection and estimation of patient specific parameter values for the physiological models, the quality of the physiological models fit to all data can be assessed. This is performed by entering ventilator settings (f, Vt, FiO_2) identical to those displayed in the column labelled "Current" into the column labelled "Simulated" and clicking the simulate button. The result of the simulation is displayed in the columns labelled "Simulated" and the quality of fit can be assessed by comparing these results to the values in the column labelled "Current" in the RHS. When the model fits well the values in the "Current" and "Simulated" columns are similar, as in the patient example illustrated in figure 9. A poor fit illustrated by differences between current and simulated values would indicate errors in data collection or parameter estimation and imply that the DSS cannot be used for simulation or to provide advice in the specific patient.

Step 3: Clinical use of the DSS INVENT

Following the parameter estimation and quality of fit assessment, INVENT can be used to support in the process of selecting ventilator settings. The clinician can perform simulations of the effect of various combinations of FiO_2, f and Vt reflected in the values of PIP, SaO_2, PaO_2, PCO_2, pH and SvO_2. The DSS can, in addition, be requested to provide advice for ventilator settings of FiO_2, f and Vt, a process where the DSS automatically searches through various combinations of FiO_2, f and Vt using a gradient descend method, identifying the values resulting in minimum total penalty. Currently the physiological models

included in INVENT cannot simulate the effect of changes in PEEP and I:E-ratio and values of these remains fixed to those selected by the clinician.

2.4 Patient material

2.4.1 Retrospective evaluation of the feasibility of INVENT in a homogeneous, well-monitored patient group of post-operative CABG patients

Data from 20 patients (male, mean age 65 years, range 38-68) were retrospectively collected from a previous study conducted following uncomplicated CABG with cardio-pulmonary bypass, with these data sets including measurement of mixed venous blood gases [65]. The study had been approved by the committee of North Jutland and Viborg Counties. Signed informed consent had been obtained from all patients. The patients were mechanically ventilated using a controlled mode, i.e. pressure regulated volume control (PRVC) mode (Maquet Servo 300, Solna, Sweden). Ventilator settings were selected by the attending intensive care clinicians, with none of the clinicians being involved in the development of the DSS. All patients had as routine monitoring an intra arterial-line and a pulmonary arterial catheter.

For the patients median PaO_2/FiO_2 was 38.8 [27 – 55] at a mean FiO_2 level of 39.9 ± 5 %, and a mean SaO_2 of 96.7 ± 1.3 %.

2.4.2 Retrospective evaluation of the feasibility of INVENT in severely ill patient cases

Data from 9 mechanically ventilated ICU patients (7 male, mean age 64 range 51-74) were retrospectively collected from a previous study [68].Patients were mechanically ventilated using a controlled mode and considered haemodynamially stable (s-lactate < 4 mol/l, base excess > -6). The study had been approved by the ethical committie of North Jutland and Viborg Counties and the ethical committee of Copenhagen. Informed written and oral consent was obtained from next of kin. In 7 of the 9 patients data measurements were performed at two different PEEP levels within the same day. Data from both

PEEP levels were included and as such, a total of 16 patient cases were included in the evaluation.

All patient cases had compromised lung function due to primary lung infections or secondary to severe sepsis or septic shock with a mean PaO_2/FiO_2 of 21.4 ± 4.6 kPa, at mean FiO_2 51 ± 10 %, and mean SaO_2 of 96.6 ± 2.5%.

2.4.3 Evaluation of whether the model of clinical preference is an adequate representation of clinical opinion.

Patient cases were selected from previously conducted studies [47,66] to reflect a broad range of respiratory, circulatory and metabolic status in patients suffering from ALI and ARDS. The studies had been approved by the ethical committee of North Jutland and Viborg Counties and the ethical committee of Copenhagen.

Table 1 - *Parameters values of the mathematical models describing lung function, metabolic function, and circulatory state*

Case	Shunt (%)	fA2/ΔPO_2 /kPa	V_D (l)	Cdyn (ml/cmH_2O)	CO (l/min)	VO_2 (l/min)	VCO2 (l/min)
1	28	0.12/17.6	0.21	33	6.0	0.208	0.133
2	18	0.30/6.5	0.25	29	7.0	0.305	0.239
3	16	0.22/10.6	0.25	29	5.9	0.323	0.227
4	27	0.13/8.5	0.21	21	5.8	0.158	0.163
5	46	0.11/21.3	0.23	21	6.6	0.145	0.097
6	31	0.10/22.6	0.25	62	5.8	0.240	0.137
7	24	0.33/5.1	0.19	26	5.4	0.269	0.192
8	20	0.49/2.5	0.16	40	5.5	0.236	0.200
9	19	0.58/3.1	0.37	58	6.1	0.236	0.205
10	12	0.27/10.4	0.20	31	5.7	0.369	0.250

V_D: anatomical dead space; fA2: fractional ventilation distribution; ΔPO_2: alveolar to end-capillary oxygen pressure drop; Cdyn: dynamic compliance CO: cardiac output; VO2: oxygen consumption; VCO2: carbon dioxide production.

For the evaluation, ten patient cases were selected as a pilot study had shown that this was the quantity possible to achieve during an hour of concentrated work. As illustrated in table 1, the patients' status were described by the parameter values of the physiological models, with patient cases representing: moderately to substantially increased shunt and V/Q mismatch; normal to increased dead space; low to normal Cdyn; decreased to increased CO; and normal to high VO_2 and VCO_2.

2.5 Evaluation procedure

2.5.1 Retrospective evaluation of the feasibility of the DSS INVENT in a homogeneous, well-monitored patient group of post-operative CABG patients

From a previously conducted study data measured 4 hours post-operatively were retrospectively collected for each patient to enable description of ventilatory, circulatory and blood state including variation of FiO_2 in 4-6 levels. Vt, f, PEEP, PIP, I:E-ratio were retrieved from the ventilator (SV300 Marquet, Solna, Sweden). SpO_2, $FetO_2$, FiO_2 measured by pulse oximeter and side-stream analyser (Anaesthetic Gas monitor type 1304, Brüel & Kjaer, Denmark). As routine monitoring of these CABG-patients included a pulmonary artery catheter (PAC) a mixed venous blood gas sample were drawn and CO were measured by thermal dilution (Continuous Cardiac Output, Edwards Life Science LLC, Irvine, USA). SaO_2, PaO_2, $PaCO_2$, pHa SvO_2, PvO_2, $PvCO_2$, pHv, Hb, COHb and MetHb were measured from the blood samples (ABL 525 or 725 Radiometer Medical A/S, Copenhagen, Denmark) and entered manually into the DSS. Values of Hb, COHb and MetHb were measured in mixed venous blood. In addition, mixed venous blood gas values were used to calibrate the ODC and estimate the value of DPG.

The data for each patient were input into the DSS according to the three steps as described in section 2.1.3 for "situation 1". In step 1 the physiological models were tuned to the individual patient by estimation of parameter values. The quality of the model fit to the individual patient data was evaluated by

comparing model simulated values with measured patient data, and the DSS was used to suggest ventilator settings. The DSS' advice was evaluated comparing the suggested values for ventilator setting (Vt, FiO_2 and f) and the simulated resulting outcomes (PIP, $FetO_2$, $FetCO_2$, SpO_2, PaO_2, PCO_2, pHa, SvO_2, PvO_2, PCO_2, pHv) to the settings and measured outcomes at the actual time of inclusion in the study selected by the attending clinician.

2.5.2 Retrospective evaluation of the feasibility of the DSS INVENT in severely ill patient cases

For each of the 16 patient cases data were collected retrospectively to enable description of ventilatory, circulatory and blood state including the data obtained from the variation of FiO_2 in 4-6 levels. These data were obtained as follows. Vt, f, PEEP, PIP, I:E-ratio were measured by the ventilator (ServoI, Marquet, Solna, Sweden). SpO_2, FiO_2 and $FetO_2$ were measured by side-stream paramagnetic oxygen analyser (Oxigraf, Mountain View CA, USA), while $FetCO_2$ and V_D were measured by the stand alone respiratory monitor (CO2SMO Plus, Novametrix Medical Systems, Wallingford CT, USA).). SaO_2, PaO_2, $PaCO_2$, pHa, Hb, COHb and MetHb were measured from blood samples (ABL 525 or 725 Radiometer Medical A/S, Copenhagen, Denmark) and entered manually into the DSS. These data were used in the DSS in three steps as described in section 2.1.3 "situation 2" to provide advice for optimal FiO_2, f, and Vt, and to simulate, for this advice, the resulting outcome values of SaO_2, PaO2, pHa, $PaCO_2$ and PIP. Vt was calculated as ml per kg of predicted body weight (PBW) to enable comparison with guidelines [11]. Average and spread have been calculated for the clinically selected ventilator setting (FiO_2, f, and Vt in ml per kg PBW) and the resulting outcomes (SaO_2, PaO_2, pHa, $PaCO_2$ and PIP), for the DSS provided advice for ventilator settings (FiO_2, f, and Vt in ml per kg PBW) and the resulting outcomes (SaO_2, PaO_2, pHa, $PaCO_2$ and PIP), and for differences in settings and outcomes between the clinical values and the DSS provide values. The values of ventilator settings from the clinic and calculated by the DSS have been evaluated for rationality, clinical relevance and soundness by comparing to the recommendations in ARDSNet guidelines [11]. To explore the variation in DSS' advice with PEEP,

the advice for FiO_2, Vt and f for each patient at the two different PEEP levels were also compared.

Cardiac output sensitivity analysis

The sensitivity of physiological parameter values and the DSS' advice to inaccuracies in measurement or calculation of CO were evaluated by estimating physiological parameter values for 5 different values of CO. As described in section 2.1.3 "situation2", the initial CO was estimated from BSA and a cardiac index of 3.7 l/min/m^2. Other values of CO used in this analysis were calculated from the initial increased and decreased by 1 and 2 l/min. A variation of 2 l/min is comparable to a variation of 20 % in a patient with a CO of 10 l/min compatible with the expected precision of ± 20 % for thermal dilution measurement of CO [67]. For each value of CO, the DSS was used in the three steps to generate advice for ventilator settings. The changes in estimated model parameters and advice for ventilator settings upon variation in CO were evaluated.

2.5.3 Evaluation of whether the model of clinical preference is an adequate representation of clinical opinion.

Experts' suggestion of ventilator settings

Ten senior intensive care clinicians from 4 university hospitals in Denmark participated in the study. Eight of the clinicians had concluded the Scandinavian Society of Anaesthesiology and Intensive Care Medicine's intensive care training programme, the remaining two had either lectured or been appointed as censors on courses incorporated in the programme. The group was therefore expected to have similar experience and possess relatively consistent opinions towards ventilator strategy. Individually, each clinical expert was presented with each of the 10 patient cases in a random order in a computer program especially designed for this study and incorporating the physiological models of the DSS INVENT (figure 10).

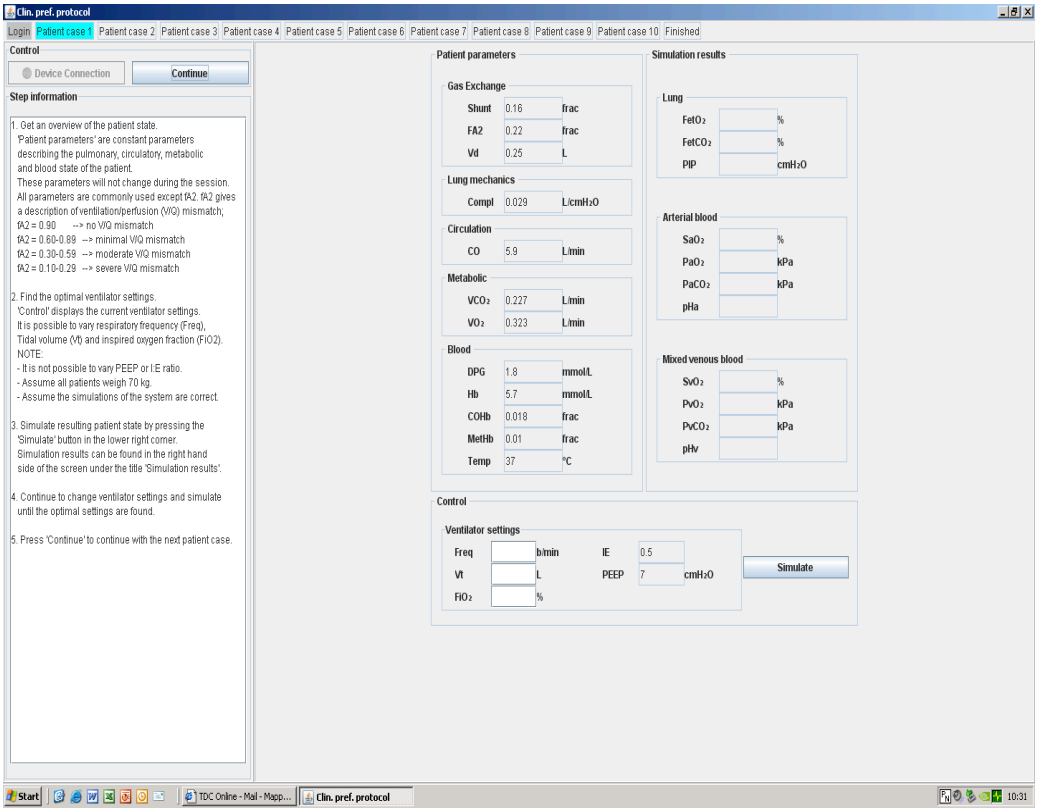

Figure 10. User interface for the data collection system, including instructions as steps, and simulation panel for each patient case. Data shown is from patient case 3, table 1.

The physiological models had for each patient case been fitted to measured patient data and the parameter values estimated, such that the programme could be used to perform simulations. The individual clinician used the programme to perform simulations of different combinations of ventilator settings (FiO_2, Vt and f) and to select the settings which to his or her opinion balanced settings and outcomes most favourable. In the procedure all clinicians had the same standardised instructions: to assume PEEP and I:E ratio set correctly; that the patients all had a standard weight of 70 kg; to assume haemodynamic stability; and to assume the model predictions to be correct.

In each patient case, the DSS was also used to provide advice for optimal settings. This resulted in a total of 110 suggestions of ventilator settings, i.e. 10 provided by clinicians plus 1 by the DSS in all 10 patient cases.

Suggestion	1			Suggestion	6		
FiO_2	60	PIP	27 good	FiO_2	70	PIP	25 good
f	18	SaO_2	94.8 acceptable	f	18	SaO_2	95.8 acceptable
Vt	542	PaO_2	8.3 unacceptable	Vt	497	PaO_2	9.4 unacceptable
I:E	1:2	$PaCO_2$	4.9	I:E	1:2	$PaCO_2$	5.6
PEEP	10	pH	7.467 Rank	PEEP	10	pH	7.413 Rank
		SvO_2	71.3			SvO_2	72.4
Suggestion	2			Suggestion	7		
FiO_2	65	PIP	24 good	FiO_2	65	PIP	25 good
f	22	SaO_2	95.0 acceptable	f	18	SaO_2	94.9 acceptable
Vt	449	PaO_2	8.8 unaccepable	Vt	497	PaO_2	8.8 unacceptable
I:E	1:2	$PaCO_2$	5.6	I:E	1:2	$PaCO_2$	5.6
PEEP	10	pH	7.418 Rank	PEEP	10	pH	7.414 Rank
		SvO_2	71,6			SvO_2	71.5
Suggestion	3			Suggestion	8		
FiO_2	70	PIP	25 good	FiO_2	60	PIP	25 good
f	20	SaO_2	96.1 acceptable	f	16	SaO_2	93.6 acceptable
Vt	497	PaO_2	9.5 unacceptable	Vt	492	PaO_2	8.3 unacceptable
I:E	1:2	$PaCO_2$	5.1	I:E	1:2	$PaCO_2$	6.2
PEEP	10	pH	7.448 Rank	PEEP	10	pH	7.377 Rank
		SvO_2	72.8			SvO_2	70.1
Suggestion	4			Suggestion	9		
FiO_2	70	PIP	23 good	FiO_2	75	PIP	25 good
f	22	SaO_2	95.2 acceptable	f	18	SaO_2	96.5 acceptable
Vt	423	PaO_2	9.3 unacceptable	Vt	498	PaO_2	10.2 unacceptable
I:E	1:2	$PaCO_2$	6.3	I:E	1:2	$PaCO_2$	5.7
PEEP	10	pH	7.374 Rank	PEEP	10	pH	7.413 Rank
		SvO_2	71.7			SvO_2	73.3
Suggestion	5			Suggestion	10		
FiO_2	55	PIP	24 good	FiO_2	80	PIP	23 good
f	18	SaO_2	92.7 acceptable	f	20	SaO_2	96.1 acceptable
Vt	465	PaO_2	7.9 unacceptable	Vt	422	PaO_2	10.4 unacceptable
I:E	1:2	$PaCO_2$	6.3	I:E	1:2	$PaCO_2$	6.9
PEEP	10	pH	7.373 Rank	PEEP	10	pH	7.341 Rank
		SvO_2	69.1			SvO_2	72.8

Figure 11. Evaluation form for a single patient case. the form presents 10 suggestions, 9 other expert's and 1 DSS of Vt, f and FiO_2 and the model simulated resulting PIP, SaO_2, PaO_2, PCO_2,pH and SvO_2. Reproduced with kind permission from Elsevier: Allerød et al. ([49]) fig.1

Experts' classification and ranking

Each clinician completed an evaluation form for each patient case (figure 11), with this form presenting blindly 10 suggestions of FiO_2, f and Vt and the settings, i.e. the selections of the 9 other clinicians and the DSS. The clinicians were as such not evaluating their own suggestions. Clinicians were presented with the evaluation forms in random case order, and with the different experts' suggestions allocated randomly on the form from case to case. Clinicians were informed that all suggestions were from experienced intensive care clinicians, and that they would not be evaluating their own suggestion. Clinicians were requested to classify each suggestion as: good, if they in a clinical setting would leave the settings unadjusted, acceptable, if they would adjust on occasion; or unacceptable, if they promptly would adjust. In addition, they were asked to rank the suggestions from 1-10, with 1 being the best.

2.6 Statistics

In the retrospective evaluation of the DSS in post-operative CABG patients mean ± SD were used to describe continuous normal distributed data and Paired t-test were used to analyse for significant difference. Continuous non-normally distributed data were described using median [range].

In the retrospective evaluation in severely ill patient cases continuous data were described using mean ± SD in normally distributed data and median (IQR) [range] in not normally distributed data. To analyse for significant differences Paired t-test was used in normally distributed data, while Wilcoxon's signed rank test was used in data sets, which had skewed distribution. In the comparison of the DSS including model simulated outcome values, and the clinically used ventilator settings including measured outcomes median and normalised interquartile range (NIQR = 0.7413*IQR) were calculated to estimate mean and SD. This to enable comparison with normally distributed values. In the evaluation of the changes in estimated model parameters and advice for ventilator settings upon variation in CO boxplots with 25^{th} and 75^{th} percentile, median, range and outliers (1.5 times interquartile range away from the box) were used to show the location and the variability of the data.

In the evaluation of the preference toward mechanical ventilator settings, the clinicians' preferences were described using median and range as the data had skewed distribution. To analyse the variation in the clinicians' preference the non-parametric Friedman test for repeated measurements was applied. Calculations were made of the percentage of classification as good, acceptable and unacceptable for each clinician and the DSS and as total. In addition, calculations were made of the average rank and range of ranks for the clinicians' and DSS' advice in the evaluation by the other experts.

3. Results

3.1 Retrospective evaluation of the feasibility of the DSS INVENT in a homogeneous, well-monitored patient group of post-operative CABG patients

As illustrated in table 2, the parameter values describing metabolism, circulation and blood were consistent with a relatively homogeneous, stable post-operative patient group. For lung mechanics, represented by Cdyn, the values are at the lower end of the normal range [68]. For gas exchange parameters: V_D, represented as a fraction of Vt, was moderately increased [69]; for shunt and V/Q mismatch the values were also moderately increased [50,54,55].

Table 2- Physiological model parameters mean values and standard deviation.

	Vd (l)	VD/ Vt	shunt (%)	fA2/ΔPO_2 /(kPa)	Cdyn (l/cm H_2O)	DPG (mmol/l)	Hb (mmol/l)	Q (l/min)	VO_2 (l/min)	VCO_2 (l/min)	RQ
Mean	0.219	0.379	15.3	0.54/2.98	0.042	4.3	5.6	5.9	0.260	0.223	0.86
SD	0.084	0.129	4.42	0.09/1.32	0.011	0.6	0.5	1.0	0.042	0.047	0.11

In the evaluation of the quality of model fit, the DSS simulated values fitted the measured values well for PIP, $FetCO_2$, $FetO_2$, $PaCO_2$, pHa, $PvCO_2$ and pHv, with mean and standard deviation of the difference between model simulated and measured values being insignificant ($P > 0.1$). For arterial oxygen saturation simulation was of SpO_2 not SaO_2 as the model was fitted to pulse-oximeter data. This resulted in no significant difference between simulated and measured SpO_2. Measurements of SpO_2 and SaO_2 were, however, significantly different with a mean difference of 1.7 ±1.4 (mean ± SD) ($p<0.001$). As the DSS assumes the simulated SpO_2 equivalent to simulated SaO_2 when calculating PaO_2, SvO_2 and PvO_2, this significant difference translates into error in simulated values of PaO_2, SvO_2 and PvO_2. The impact of this error in relation to the safety of the advice for ventilator settings provided by the DSS will be addressed in the discussion.

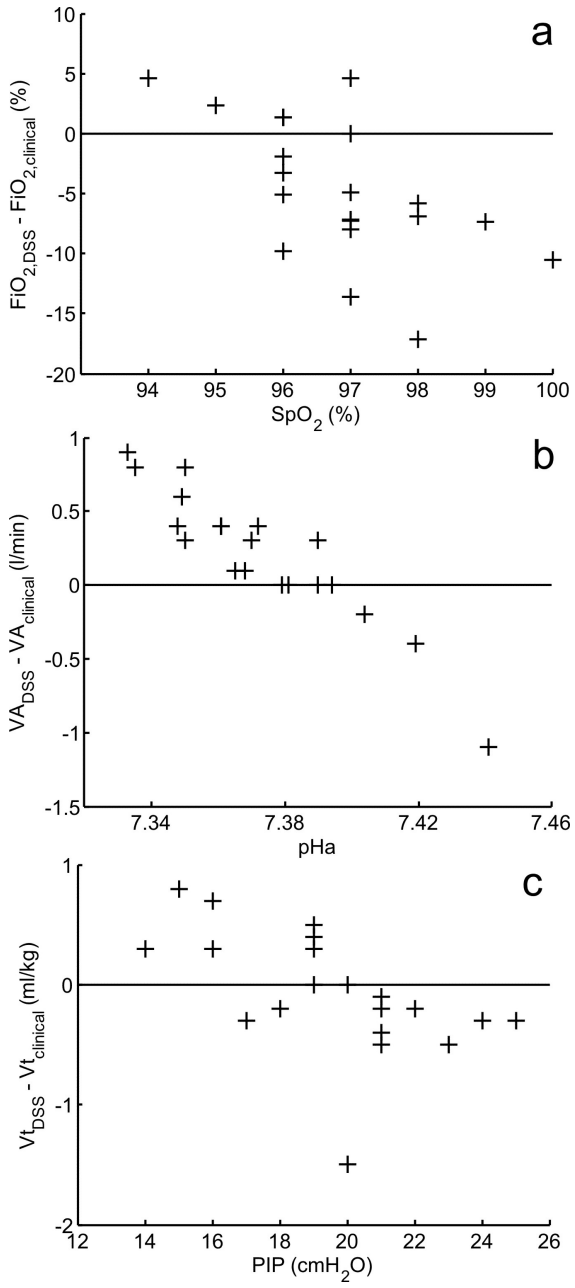

Figure 12 Bland Altman plots illustrating the relationship between: (a) measured SpO_2 and DSS suggested adjustment of FiO_2; (b) measured pHa and DSS suggested adjustment of VA and (c) measured PIP and DSS suggested adjustment of Vt which implicates decrease in situations of high levels of measured PIP and increase in low measured PIP. Reproduced with kind permission from Elsevier: Allerød et al. ([47], p. 211) Fig. 3

In step 3, the DSS was used to provide advice for FiO_2, f and Vt and these were retrospectively compared to the settings utilised by the clinicians as illustrated in figure 12. For FiO_2 INVENT suggested values in a range only slightly different from the clinicians, 27.0-44.5 % compared to 28.7-47.9 %. This resulted in simulated values of SpO_2 in the range 94.6-97.4 % and SvO_2 49.5-

77.6 %, and in measured values of SpO_2 94.0-100 % and SvO_2 50.5-78.5 %. These values compared well to clinicians' values, but with some notable differences. As illustrated in figure 12a, the DSS tended to advise on lower FiO_2 levels in situations of high SpO_2, where as it increased FiO_2 in situations with low SpO_2 providing oxygen only as necessary. Figure 12b illustrates the relationship between measured pH and the DSS suggested change in VA. The DSS suggested decreasing VA in situations with measured pH > 7.400 and increasing in situations with measured pH < 7.394. These proposed changes were suggested achieved by either changing f or Vt such that predicted PIP was equal to or below 22.9 cmH_2O and f equal to or below 18 breaths min^{-1}. Figure 12c illustrates how the DSS suggested decreasing Vt at high measured PIP level and increasing Vt at low measured PIP level.

3.2 Retrospective evaluation of the feasibility of INVENT in severely ill patients

As illustrated in table 3, lung function was compromised in these patients, as quantified by low values of dynamic compliance, large shunt fractions and V/Q mismatch represented by increased values of ΔPO_2 and ΔPCO_2 values.

Table 3 – *Physiological model parameters.*

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

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

In general, the physiological models provided a good description of the patients' data with only minor differences between measured and model simulated values (Table 4). For $FetO_2$ and PaO_2 differences were, although small, significant ($p < 0.05$). In four cases, PaO_2 difference was ≥ 1 kPa, however measured and simulated PaO_2 were above 10 kPa in these cases, indicating sufficient oxygenation.

Table 4 – *Differences between model simulated and measured values.*

Value	n = 16
PIP (cm H_2O)	0.0 (0.0 – 0.0) [-1.0 – 1.0]
$FetCO_2$ (%)	0.0 ± 0.2
$FetO_2$ (%)	0.2 ± 0.4*
SaO_2 (%)	0.0 ± 0.6
$PaCO_2$ (kPa)	0.0 ± 0.2
PaO_2 (kPa)	0.2 (-0.1 – 1.0) [-0.4 – 2.8]*
pHa	0.00 ± 0.01

Summarised as mean ± SD or median (IQR) [range]; *: $p < 0.05$.

Figure 13 illustrates INVENT's advice for FiO_2, f and Vt in combination with the resulting model simulated outcomes. Figure 13a illustrates the advice for FiO_2 and resulting simulated SaO_2. The advice can be seen as rational as lower FiO_2 levels were suggested in patient cases with high SaO_2, while high FiO_2 levels were suggested in patient cases with low SaO_2. Figure 13b illustrates the advice for minute ventilation (Vmin) and resulting model simulated pHa levels. The DSS balanced prevention of acidosis and alkalosis against high Vmin, and as such prevented high Vt and f, accepting lower pH as an alternative to increasing Vmin. Figure 13c illustrates the advice for Vt and resulting model simulated PIP level. INVENT only suggested high Vt in patient cases with low PIP.

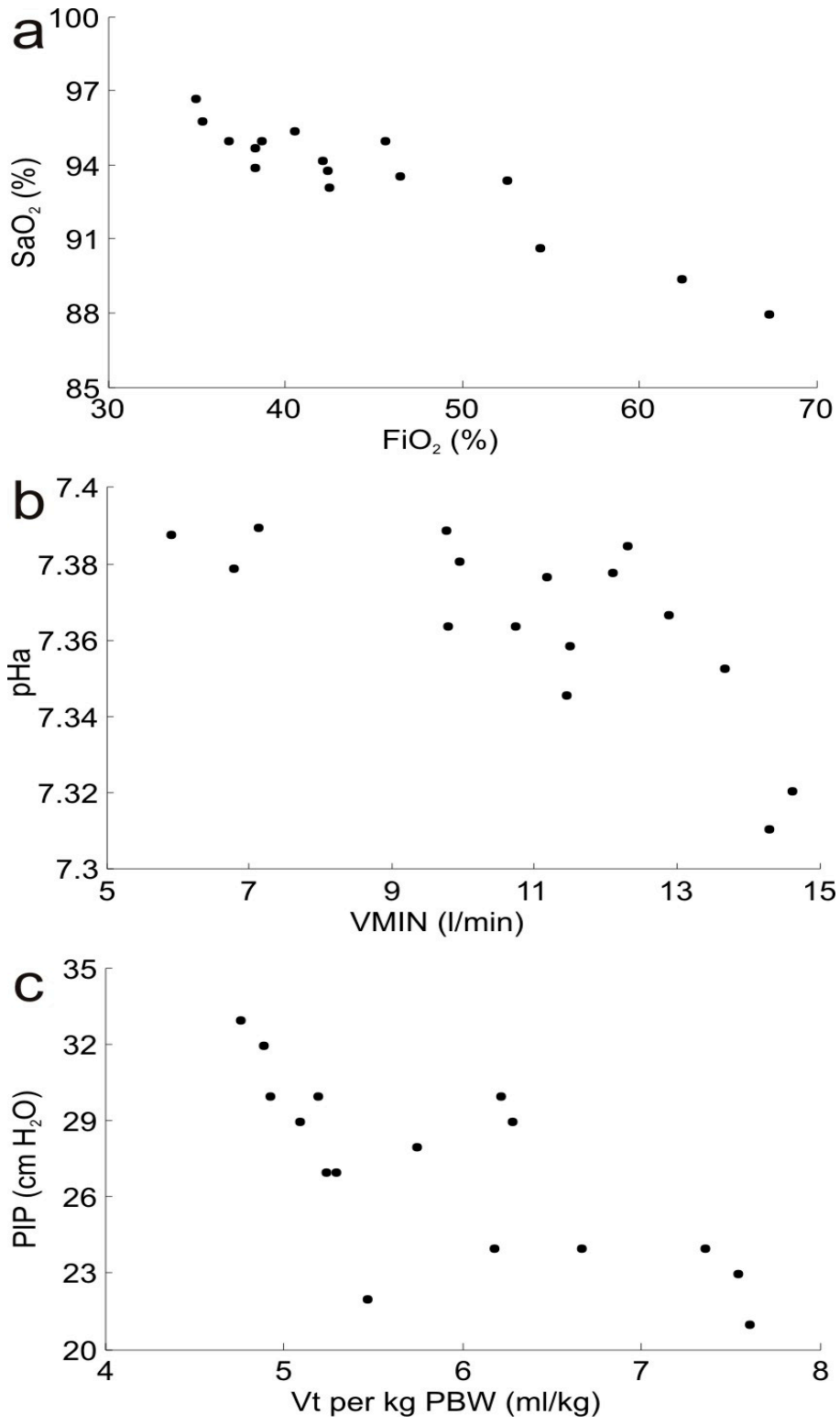

Figure 13. DSS provided advice and resulting model simulated outcomes for: a) Inspired oxygen fraction versus arterial oxygen saturation; b) Minute volume versus arterial pH; c) Tidal volume versus peak inspiratory pressure. Reproduced with kind permission from Springer + Business Media: Karbing et al. ([48] p.47) Fig. 2

To evaluate not only if the advice provided by the DSS was rational but also clinically reasonable, INVENT's advice and the resulting model simulated outcomes have been compared to the ARDSNet recommendations [11]. This was also performed for the clinically used ventilator setting and the measured outcome to similarly evaluate how reasonable clinical settings were.

Table 5 – DSS advice and model simulated outcome.

Value	Clinical[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 [298 – 571]	-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 [17 – 36]	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 [21 – 33]	-5 ± 3

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

[a] clinically selected settings (FiO2, Vt and f and PEEP) and measured values of SaO_2, PaO_2, pHa, $PaCO_2$ and PIP

[b] DSS advice of FiO2, Vt and f, clinically selected level of PEEP; models simulated values of SaO_2, PaO_2, pHa, $PaCO_2$ and PIP

[c] Differences between DSS provided advice and resulting model-simulated outcome and the measured clinically selected settings and measured SaO_2, PaO_2, pHa, $PaCO_2$ and PIP

For oxygenation the ARDSNet recommendations are PaO_2 55 – 80 mmHg (7.3 -10.7 kPa) and SpO_2 88 - 95 %. As illustrated in table 5 clinically baseline average values of SaO_2 and PaO_2 were near or above the ARDSNet

recommendation. Generally the DSS advised decreasing FiO_2 with the majority of simulated values of PaO_2 and SpO_2 being within the ARDSNet Recommendation, and with no simulated values of SpO_2 being below 88 %. ARDSNet recommend a Vt of 6 ml/kg per kg PBW with a maximum of 8 ml/kg, a maximal f of 35 breath per min and pH within 7.30 – 7.45. For clinical baseline the average Vt was high, i.e. 7.9 ml per kg PBW, f well within recommendations and pH also comparing well to recommendations with average ±1 SD being within recommended range. The DSS suggested Vt of an average of 5.9 ±1.0 ml per kg PBW and never above the 8 ml per kg PBW. For pH, all DSS advice was within the ARDSNet range, and for f only a single piece of DSS advice was above the recommended maximum, i.e. 36 breaths per min. While not directly comparably, the clinical baseline and DSS PIP values can provide an indication of the degree of compliance with the ARDSNet recommendation of plateau pressure of no more than 30 cmH_2O. For clinical baseline the PIP was on average 32 cmH_2O, while the DSS advice gave simulated PIP values of on average 27 cmH_2O with no values exceeding 33 cm H_2O (figure 13)

Table 6 illustrates the effect of PEEP variation on the advice provided by the DSS. In 7 of the 9 patients PEEP was changed. Increased PEEP resulted in reduction in pulmonary shunt fraction (Qs/Qt or fs) in all but one patient (pt 7). This reduction in shunt improved oxygenation resulting in the DSS advising on a reducing FiO_2 by on average 6.2 % [0.4 – 11.9 %]. In patient 7 pulmonary shunt fraction increased, resulting in the DSS advising an increase in FiO_2 of 5 %. Increased PEEP resulted in change in Cdyn with a decrease in three patients (3, 5 and 7), an increase in two patients (2 and 4) and effectively no change in the remaining two patients (6 and 8). In the patients where Cdyn increased the DSS responded by advising on an increase in Vt to improve pH. In the three patients where compliance decreased the DSS advised lowering Vt, increasing f whilst accepting lower pH. In response to variation in PEEP, the DSS advice and resulting model simulated outcomes behaved in adherence with the recommendation of the ARDSNet except in one case where f was 36 breaths per min, i.e. 1 too high (Table 6).

Table 6 – DSS advice upon changes in PEEP.

Pt	PEEP cmH_2O	Cdyn ml/cmH_2O	Shunt %	FiO_2 %	Vt ml/kg	f min^{-1}	SaO_2 %	pHa	PIP cmH_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; Cdyn: Measured dynamic respiratory compliance; Shunt: Model fitted shunt parameter; FiO_2, Vt ml per kg PBW and f: DSS advice; SaO_2, pHa, and PIP: Model simulated values resulting from INVENT's advice.

Cardiac output sensitivity analysis

Figure 14 illustrates box-plots of variation in model parameters and the DSS advices for FiO_2 in response to variation in CO. Shunt values changed with CO but this was not substantial as the average change in shunt was 2 % per 1 l/min change in CO. For the other model parameters and the advice for FiO_2, changes were negligible except in a few patient cases where either ΔPO_2 or FiO_2 varied

substantially. These patient cases were characterised by increased VO_2,demanding an equally increased oxygen delivery to prevent hypoxaemia.

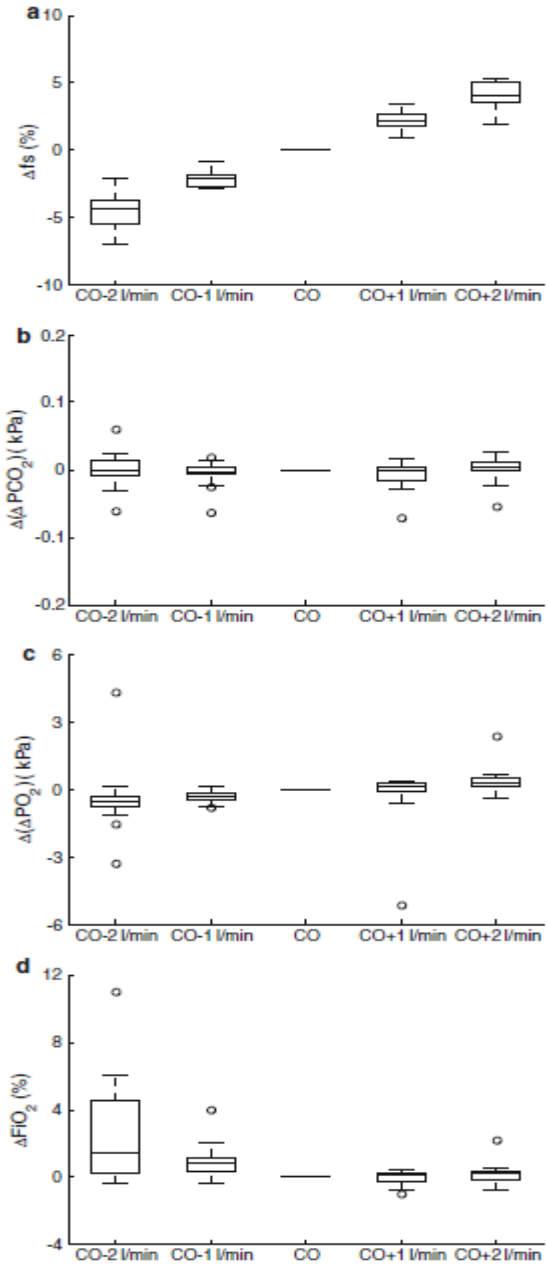

Figure 14 Boxplots of variations in model simulated parameters and advice in CO from baseline ((baseline CO = BSA*3.7 l/min/m^2). Boxes represents the 25^{th} to 75^{th} percentile of data, *horizontal line in boxes* represents the median, *dashed line with whiskers* represents represent range excluding outliers. Outliers are points more than 1.5 times the inter-quartile range away from the box. Outliers are illustrated individually by *circles*. **a** Changes in the shunt model parameter (Δfs). **b** Changes in ΔPCO2 model parameter ($\Delta(\Delta PCO_2)$). **c** Changes in ΔPO_2 model parameter ($\Delta(\Delta PO_2)$). **d** Changes in DSS advice for FiO_2 (ΔFiO_2). Reproduced with kind permission from Springer + Business Media: Karbing et al. ([48] p.49) Fig. 2

For Vt and f the variations upon changes in CO were small, as the ranges of variation were within -4 to 10 ml and 0 to 1 breath per min, respectively.

3.3 Evaluation of whether the model of clinical preference is an adequate representation of clinical opinion.

The variability of each of the 10 clinicians and DSS's preference towards ventilator settings (FiO_2, Vt and f) and the simulated results (SaO_2, PIP and pH) over all patient cases are illustrated in figure 15. The clinicians' preferences varied significantly from each other ($p < 0.005$). However, for 5 of the clinicians (3-5, 6-7), the median value of Vt was the same, i.e. Vt = 0.500 l, and 2 of the clinicians (8,9) preferred Vt of 0.420 l, i.e. 6 ml/kg in either 8 or 9 of the 10 patient cases respectively.

Figure 16 illustrates for each patient case the range of selected FiO_2, f and Vt, and the simulated results of these selections on SaO_2, PIP and pH. In all patient cases, FiO_2 variability was large, i.e. from a median of 0.45 and a range of 0.40-0.60 in patient case 4, to a median of 0.75 and a range of 0.60-0.99 in patient case 5. The resulting simulated SaO_2 varied in both these cases more than 4.5 %. In all patient cases, the DSS suggested FiO_2 and resulting simulated SaO_2 values were below median. For Vt suggestions varied from a range of 0.390 l to 0.420 l in patient case 5, to a range of 0.420 l to 0.720 l in patient case 6. In patient cases with low pulmonary compliance the variability of Vt values was small, e.g. patient case 4, and all experts including the DSS preferred low Vt to reduce values of PIP. This was in contrast to patient cases with relatively normal pulmonary compliance where Vt variation was very high, e.g. patient case 6 and 9. In these cases, some experts and the DSS allowed higher values of Vt to normalise pH, where others preferred preserve low Vt, either accepting relatively low values of pH values or increased respiratory frequency. Values of respiratory frequency varied from 16 breaths pr min to 22 breaths pr min in patient case 1, to 14 breaths pr min to 44 breaths pr min in patient case 9. The variability in Vt and f resulted in variation of simulated values of PIP with a maximum variation of 24 cm H_2O to 33 cm H_2O in patient case 7, with the value for the DSS being at the median, i.e. 27 cm

H_2O. pH varied with a maximum variation of 7.29 to 7.44 in patient case 9, with the resulting simulated value for the DSS at the median, i.e. 7.39.

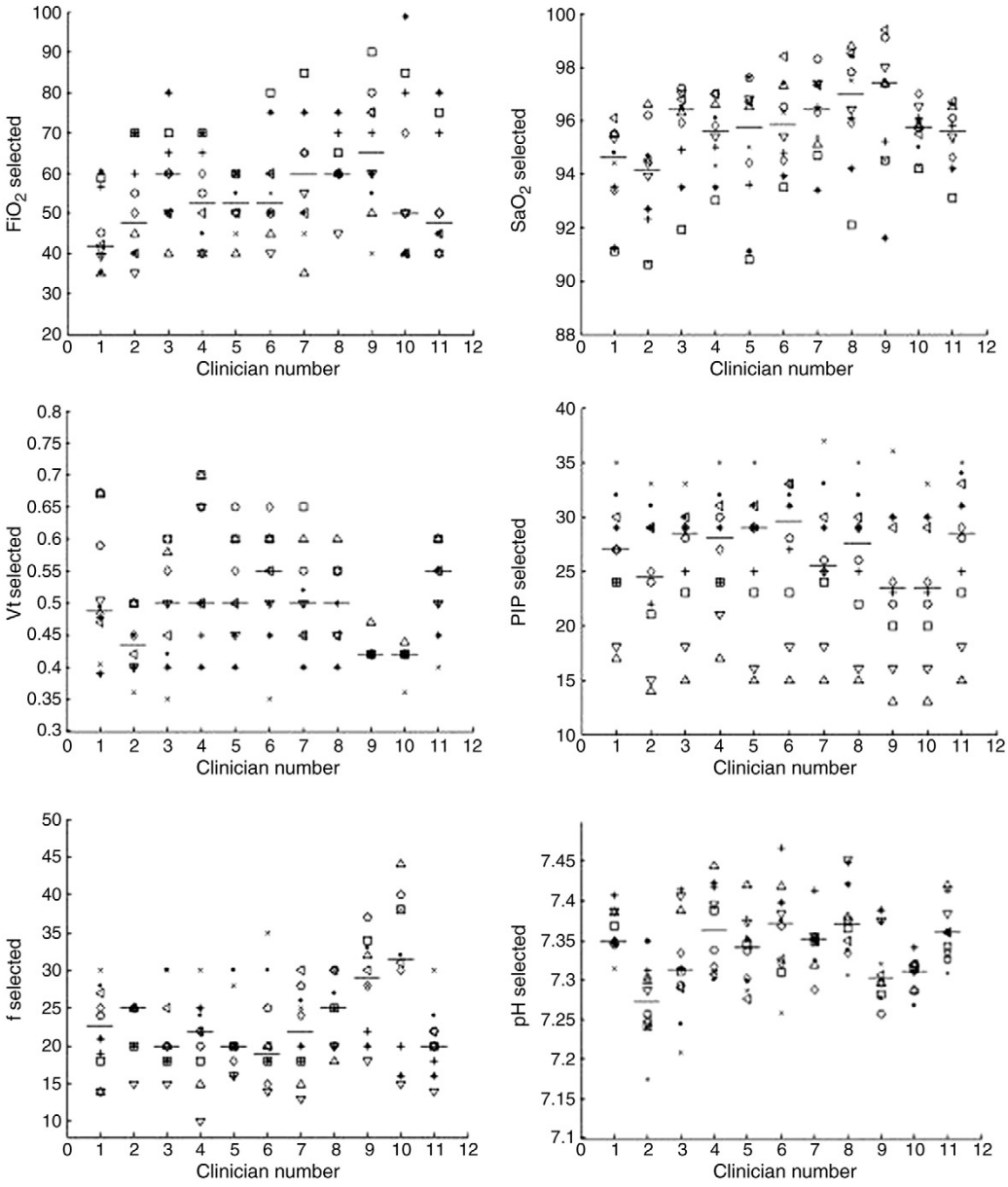

Figure 15 Illustration of the variability of INVENT's (depicted as clinician 1) and each of the 10 clinicians' preferences towards ventilator settings (FiO_2, Vt, and f) and resulting simulated values of SaO_2, PIP and pH over all patient cases. Each symbol represents a single patient case; horizontal lines represent median values. Reproduced with kind permission from Elsevier: Allerød et al. ([49]) Fig. 2

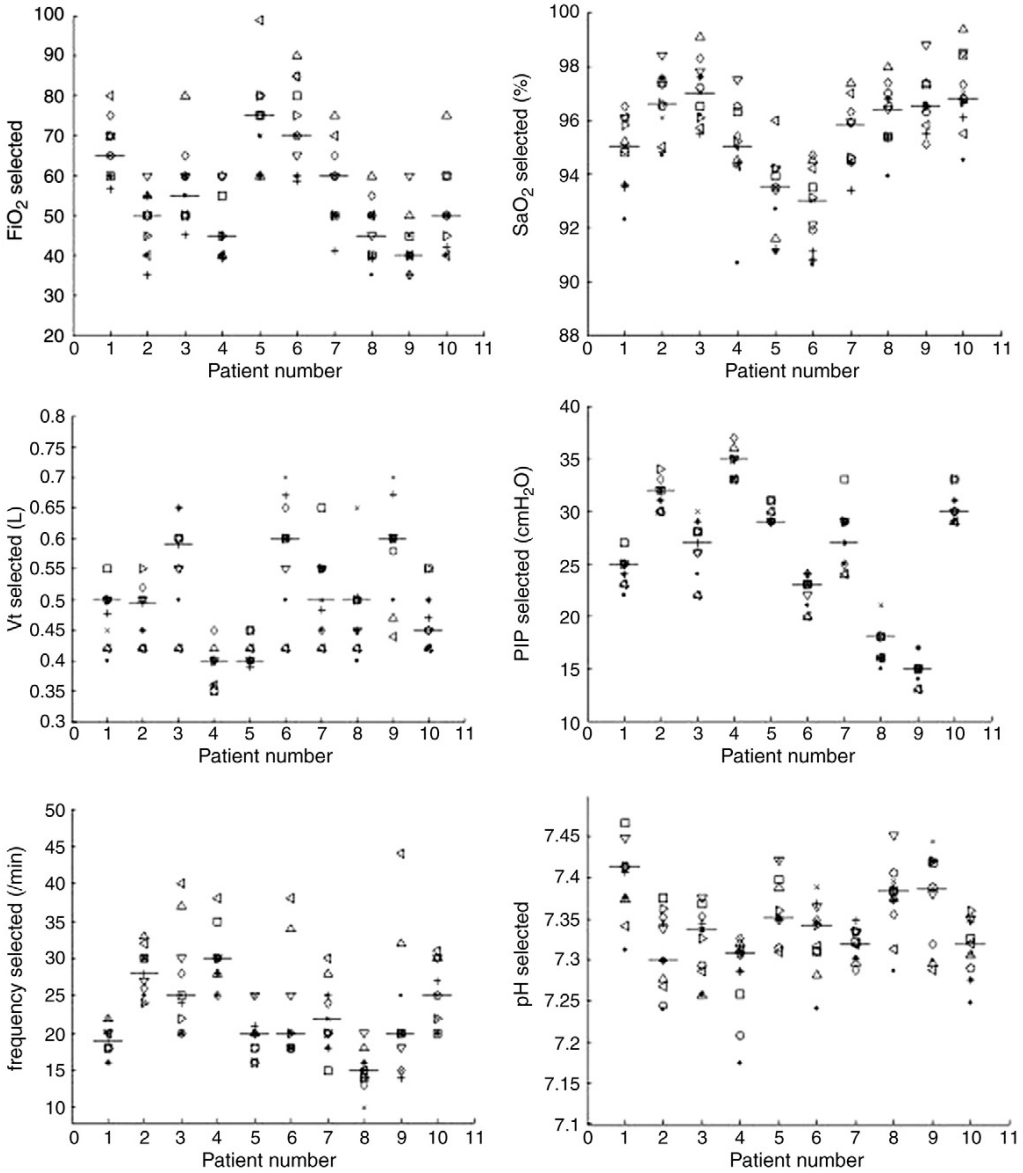

Figure 16 Illustration of variability of the suggested ventilator settings of FiO_2, f and Vt and the resulting model simulated values of SaO_2, PIP and pH for each of the 10 patient cases, overall clinicians and INVENT. Values of INVENT are illustrated by crosses (+), each of the other symbols used represents a single clinician, the horizontal lines represent median values. Reproduced with kind permission from Elsevier: Allerød et al. ([49]) Fig. 3

Table 7 presents the results of the classification procedure. The clinicians generally had poor opinion of each other's and the DSS' advice, with on average considering other experts' advice to be unacceptable in 33.3 % of cases and only good in 21.2 %. The specific result for classification of the DSS was similar to this average as can be seen in column 1, table 7.

Table 7 Classification of advice for ventilator settings provided by clinicians and DSS

Expert	DSS	1	2	3	4	5	6	7	8	9	10	Average
Classification												
Good	26.0	9..9	25.5	17.6	22.1	18.8	25.4	17.6	22.0	23.3	25.5	21.2 (%)
Acceptable	41.0	49.0	46.7	45.5	44.5	45.4	45.4	56.8	43.1	36.4	46.3	45.4 (%)
Unacceptable	34.0	38.8	28.7	35.7	33.2	35.4	28.8	25.4	35.4	39.9	30.9	33.3 (%)

Table 8 presents the average rank score for each of the clinicians and the DSS. If all clinicians had agreed on the best and worst advice, the average rank would have covered the full range from 1 -11. It is therefore notable that the results have a narrow range i.e. 5.0 to 7.1. The DSS had an average rank of 5.3.

Table 8 Average and range of rank for each of the clinicians (1-10) and DSS

	DSS	1	2	3	4	5	6	7	8	9	10
Average rank	5..3	6..5	5..5	6.7	5.0	6..3	5.4	5.4	6.7	7.1	5.1
(rank range)	(3-10)	(1-10)	(1-10)	(1-11)	(2-10)	(1-11)	(1-11)	(1-9)	(1-11)	(2-10)	(2-9)

Chapter 4 Discussion

Mechanical ventilation is one of the core supportive therapies in intensive care medicine. Identification of appropriate settings can be difficult but remains important, as inappropriate ventilator settings have been shown to increase patient mortality [10,11]. To aid in the process of mechanical ventilation, decision support systems have been developed with the majority, including those brought into clinical practice, being rule-based systems. An alternative approach to decision support based on physiological models and decision theory has been proposed with these having potential advantages over rule-based systems. Model based systems can be tuned to the individual patient enabling the system to provide patient specific advice and to perform "what if" questions such that the effect of different ventilator settings can be explored. In addition, as the systems separate physiological knowledge and clinical preference the latter can be modified to emulate local intensive care clinicians' preference or according to new results from clinical trials. Such a system is however, expensive to develop, as the physiological models must be sufficiently complex, and be tuneable to the individual using routinely available clinical measurements. In addition, the model of clinical preference must represent clinical opinion in different types of patients.

This thesis has addressed whether it is feasible to develop a model based decision support system which, based on input from routine clinical monitoring, can provide reasonable advice for ventilator settings in a range of patients and in addition, adequately capture clinical preference.

This has been addressed by presentation of the DSS INVENT based on physiological models and a model of clinical preference including penalty functions in a classical decision theoretic approach. The presentation has included a description of the structure, the physiological models and the model of clinical preference. The focus of this thesis has been on the retrospective evaluation of this system and on the evaluation of the systems penalty functions. The DSS has been retrospectively evaluated in two different groups of patient cases, a group of well-monitored stable post-operative CABG patients with minimal to moderate lung problems and a group of severely ill

patient cases suffering from ALI /ARDS. The ability of the model of clinical preference to represent clinical opinion on ventilator settings has been evaluated in a comparative study with 10 clinicians on a standardised set of 10 patient cases.

The physiological models can be used to estimate patient specific parameter values describing clinical status of gas-exchange and -transport, circulation and metabolism. To support the clinician in the process of selecting ventilator setting, the physiological models, including the patient specific parameter values, can be used to simulate the effect of different ventilator settings. In combination with penalty functions in the model of clinical preference, the DSS can quantify the expected utility of the different combinations of FiO_2, Vt and f and thereby make explicit the compromises, which are present in selecting ventilator settings. In addition, INVENT can identify the combination of FiO_2, Vt and f incurring the minimum total penalty and providing these as advice for optimal ventilator settings.

In the process of retrospective evaluation of the DSS a number of necessary improvements to both the models and the physiological parameter estimation system were identified, these being related to the availability and use of clinical measurements and the generality of the physiological models and penalty functions. These improvements are illustrated in differences between the more simple and complex model fitting strategies of section 2.1.2 and in "situation 1" and "situation 2" in step 1 of the use of the DSS. As the structure of the DSS separates physiological knowledge from clinical preference, modifications of the different models could be implemented without re-design of the other models. These modifications between "situation 1" and "situation 2" are considered in turn in the following text.

In the study of the feasibility of the DSS in stable post-operative CABG patients suffering only from minor lung problems, the physiological models describing V/Q mismatch by $fa2/\Delta PO_2$ with fixed perfusion to the ventilated compartments provided a good description of the patients' states. This patient group is, however not comparably to the majority of patients ventilated in the

ICU. For patients with significant respiratory failure such as ALI and ARDS, a model of oxygen and carbon dioxide transport and storage with added complexity, describing V/Q mismatch by $fa2/\Delta PO_2$ and $f2/\Delta PCO_2$, was implemented in the DSS and used in the study evaluating the feasibility in severely ill patient cases.

In the process of estimating physiological parameters describing gas exchange (Qs/Qt (fs), $fA2/\ \Delta O_2$), the oxygen model was in the evaluation in the first patient group, i.e. stable post-operative CABG patients, fitted to pulse oximetry data, and not to the single arterial blood gas measurement of SaO_2, i.e. "situation 1". This resulted in the model fitting SpO_2 values well but with differences between model simulated and measured values of SaO_2, PaO_2 and SvO_2. Despite these differences, all patients had simulated SpO_2 above 94 %, a value, which should be adequate to ensure SaO_2 above 90 % [70], i.e. a value which can be considered safe [11]. However, as a single arterial blood gas sample is a routine clinical measurement the parameter estimation technique was modified to include fit of both SaO_2 and SpO_2 and in addition one $PaCO_2$-$FetCO_2$ data set. These measurements were in "situation 2" used in the model of oxygen and carbon dioxide transport and storage to estimate Qs/Qt (fs), $fa2/\Delta PO_2$ and $f2/\Delta PCO_2$ [59]. This modified technique was applied in the retrospective evaluation in the second group of patient cases, i.e. severely ill patients. This resulted in a minimal difference between measured and estimated SaO_2 [48]. For PaO_2 difference remained in some cases significant ($\geq$ 1 kPa in 4 of 16 patient cases). However, this was only the case for PaO_2 values above 10 kPa indicating safe levels of oxygenation.

For the model of clinical preference, it is essential to note that penalty functions are by nature subjective and that the functions currently represent the opinion of one clinician, the author. The explicit formulation and quantification of clinical preference means, however, that clinical opinion can be discussed and this may perhaps encourage a consensus process. For different sets of patient cases and/or different clinicians redefinition and rescaling of the penalty functions may be required. In the retrospective evaluation, the penalty functions had initially been defined and scaled for a set of relatively stable patient cases.

These penalty functions did however not provide adequate trade-offs between conflicting goals at higher respiratory pressures. Therefore, the penalty function for baro/volutrauma was redefined and the four penalty functions rescaled according to each other and the modified functions implemented in the DSS prior to evaluation in the severely ill patient cases. It has previously been shown, that rescaling of penalty functions may be automated deriving penalty functions from clinical opinion expressed in a set of patient cases [70].

The DSS was evaluated retrospectively in homogeneous, well-monitored patient group, ventilated using a controlled mode and generally considered uncomplicated to ventilate. In twenty uncomplicated post-operative coronary artery bypass graphing (CABG) patients, INVENT provided reasonable advice for f, Vt and FiO_2, consistent with clinical settings and with maintaining sufficient oxygenation whilst reducing risk of oxygen toxicity, normalising pH and achieving low values of PIP. This study illustrated that it is feasible to use physiological models to both describe patient's state and provide reasonable advice on ventilator settings.

While the system's advice was consistent with clinical settings, some differences were present which require further consideration here. For f and Vt INVENT's advice was, in some patients, different from the values used by the clinicians. However, in all patients, the predicted pH was in the range 7.368 to 7.404 and in all but 2 patients the DSS suggested Vt below or equal to 8 ml/kg. For the two patients, where the DSS suggested Vt above 8 ml/kg, predicted PIP was low, i.e. 14.5 cmH_2O and 21.9 cmH_2O. For f the advice was never above 18 breaths /min, meaning that the risk of air trapping was minimal.

The DSS was evaluated retrospectively in a severely ill ICU patients cases suffering from ALI or ARDS regarded as difficult to ventilate. In 16 ALI/ARDS patient cases the modified physiological models were shown to adequately describe complex lung abnormalities. Compared to the post-operative CABG patients the patient cases had on average a 10 % higher shunt, higher V/Q-mismatch indicated by on average a 3 kPA higher ΔPO_2, and an on average 15 ml/kg lower compliance. The advice provided for f, Vt and FiO_2 can

be considered both rational and clinically reasonable. Rational, as the DSS only advised on high levels of FiO_2, Vmin and Vt in patient cases with respectively oxygenation problems, acidosis and low PIP; and clinically reasonable, as the advice and the model simulated outcomes were in-line with the recommendations of ARDSNet guidelines for mechanical ventilation [11]. This latter point showing that the penalty functions version 2 could adequately describe the trade-offs at high ventilatory pressure.

As described in the presentation of INVENT the system is limited by not being able to provide advice for appropriate setting of PEEP. This evaluation has shown that, while not providing advice for PEEP, the DSS responds to changes in PEEP by both capturing the quantitative effect of PEEP on the lung function and adequately adjusting the ventilator advice.

The assumption of a constant CO is not valid for a heterogeneous group of severely ill patients and the sensitivity of both the estimated physiological model parameters and the advice for ventilator settings must be evaluated. As presented in the results, the evaluation of the DSS in the severely ill patient cases included a sensitivity analysis to variation in CO by maximally plus minus 2 l /min. Of the parameters describing gas-exchange only shunt changed with CO but to a small amount. The DSS' advice was insensitive to CO except in patient cases with elevated metabolism and where compromised circulation could be suspected. In such cases, it can be argued that measurements of CO are clinically indicated. It is important to note, that this analysis does not provide any information as to how therapeutic manipulation of CO alters pulmonary shunt. Such an intervention changes the physiological status of the patients and requires the system be re-tuned to patient state, this being possible by re-estimating model parameters.

The ability the model of clinical preference to adequately represent the opinion of a group of intensive care clinicians has been analysed. Standardisation of this analysis was possible through using the physiological models included in INVENT to present clinically patient cases and perform simulation of the outcomes of different combinations of FiO_2, f and Vt. Opinion on the same

patient cases for preferred combination of settings and outcomes could then be obtained from different clinicians, thereby separating true discrepancy in clinical opinion from variability in patients' physiology. The evaluation shows large variability as to opinion toward the best combination of FiO_2, f and Vt. This apparent lack of clinical consensus was further substantiated by the results of the classification procedure, i.e. participating clinicians considered each other's and INVENT's suggestions unacceptable in more than 30 % of the cases. In the ranking procedure, there was no consensus as to the best or worst advice and the DSS was again evaluated comparable to the clinicians.

These results indicated an apparent lack of consensus in clinical preference even when variation that could be due to difference in patient material have been eliminated. In particular, the results indicated an apparent lack of consensus on the fraction of inspired oxygen and in patients with normal lung compliance use of low tidal volume strategy.

For FiO_2 the variation was substantial with no apparent explanation for the difference in preference. This variation could perhaps be anticipated, as only experimental studies have shown that higher oxygen fractions have a toxic effect which might contribute to ventilator induced lung injury [72-73], and no large scale clinical studies have demonstrate the effect of FiO_2 strategy on patient outcome. While large scale studies are missing, the ARDSNet low Vt study may indicate that lower PaO_2 is safe as the lower PaO_2 associated with the use of low Vt did not impede reduction in mortality [11]. As such, it might be preferable to reduce FiO_2 aiming at suboptimal levels of PaO_2/SaO_2, while waiting for the results of studies designed to prospectively examine the role of oxygen in ventilator induced lung injury [74]. An additional benefit of a strategy of reducing FiO_2 may be reduction of the risk of developing absorption atelectasis [75].

The lack of agreement of use of low tidal volume strategy in patients with normal compliance may not be surprising, as controversy exist in the literature evaluating this topic. Both retrospective analysis [76-77] and a prospective study [78] have revealed that use of higher Vt may be associated with an

increased risk of developing ALI/ARDS. However, an analysis has also indicated that patients suffering from ALI but with higher pulmonary compliance may have an increased mortality when receiving low Vt ventilation [79]. In line with this latter analysis, Chiumello et al [80] have shown that similar stress and strain in the alveoli can be generated by very different tidal volumes, suggesting that higher Vt may be acceptable in patients with higher or normal compliance, or at least when functional residual capacity is closer to normal. The rational choice of tidal volume is therefore not obvious, should ARDSNet guidelines be adopted for all patients or should tidal volume be refine according to the individual patient's physiology?

The evaluation has potential limitations relating to the small numbers of clinicians and patient cases, and the use of the physiological models. 10 clinicians and 10 patient cases might be considered small for an evaluation of this type. However, 10 patient cases are about the maximum quantity a single clinician can assess in a period of 1 hour, and in the classification and ranking procedure each clinicians had to evaluate 100 patient cases. To ensure maximum information from the 10 patient cases, these were selected to represent a range of severity of ALI and ARDS. In addition, clinicians were selected to cover university hospitals in Denmark. Physiological models could be argued to be a further limitation, as these may not simulate all possible ventilator settings or strategies correctly. This was tackled by instructing the clinicians to assume that PEEP and I:E ratio were optimal and that all model predictions were correct. By doing so, the clinicians' preference towards ventilator settings were evaluated and not the correctness of the mathematical models.

This evaluation provided little information as to weather the model of clinical preference can be used in clinical practice to represent the opinion of a group of clinicians. Even among a group of clinicians with similar background, and in a procedure using the physiological models of the DSS to present the patient cases and to simulate the outcome of different combinations of FiO_2, f and Vt, enabling advice to be provided in the same cases, a lack of consensus has been shown. The DSS was evaluated with 33 % of advice being unacceptable, this

being comparably to how clinicians evaluated each other. Currently it is not obvious how the preference function should be improved. However, using the DSS with the physiological models may have the benefit of making divergence in preference explicit such that controversies can be elucidated through discussion and a consensus perhaps reached. This will be further discussed when addressing limitations of the DSS.

The current version of the DSS INVENT and the evaluation have some limitations which are consideration here. Aside from the evaluation by Karbing et al. [81], not included in this thesis, the evaluations have been performed retrospectively. As such the advice provided by the DSS has not been applied to the patients and it is not known whether patients would have behaved as simulated by INVENT. One factor that could make simulations erroneous is that model parameters remain constant on simulations implying that different combinations of f, Vt and FiO_2 do not affect the underlying physiological state of the patient. This assumption is clearly not valid for all combinations of f, Vt and FiO_2, as, for example, large perturbations in tidal volume may recruit or over distend the lung and thereby alter the underlying physiology. In practice, this could be tackled by considering the advice provided by the DSS as a "target" with this being reached in small steps controlled by the DSS including retuning of the physiological model parameters during the procedure.

The DSS does not provide advice for PEEP and I:E ratio, with the physiological models not being capable of simulating the effect of variation in these settings. The retrospective evaluation in severely ill patient cases showed that the current version responded adequately to changes in physiology on modifying PEEP. However, future studies are required to address how changes in PEEP and I:E ratio affect values of physiological model parameters describing both gas-exchange and lung mechanics, and to explore if this can be modelled [82].

In the clinical setting, the majority of intensive care patients are ventilated using assisted mode. This implies a limitation of the applicability of INVENT in its current version as advice only is provided for patients ventilated using a

controlled mode. Models are required of respiratory drive if a DSS compatible with assisted mode is to be developed [83].

For the model of clinical preference, it is essential to note that penalty functions are by nature subjective and that the functions currently represent the opinion of one clinician, the author. The retrospective evaluation of the DSS has as described above shown that reasonable advice can be provided for f, Vt and FiO_2 in homogeneous, well-monitored post-operative CABG patients and in more complex, severely ill ALI and ARDS patient cases. The apparent reasonableness of INVENT's advice in these two patient groups could lead to the conclusion that INVENT's preference functions are an adequate representation of clinical opinion. However, this is in contrast to the results of the evaluation of the model of preference, which showed lack of consensus toward a single, reasonable clinical opinion, and provided little information as to whether the DSS can be used in clinical practice. This leads to the question as to whether standardisation of a single representation of what considered reasonable is good practice? For some intensive care therapies standardization has been well accepted and shown to improve mortality statistics [18, 84-86] with variation in care being regarded to have detrimental impact on patient outcome [42,44]. To standardise mechanical ventilation therapy, e.g. lung protective ventilation, guidelines have been introduced but as described in the introduction barriers towards adherence to these have been identified [24-25]. These include lack of agreement with guidelines in general i.e. challenge to autonomy was reported, and lack of agreement with specific guidelines as low tidal volume may induce concerns in relation to patient discomfort, tackypnea, hypercapnia, acidosis and worsening of oxygenation. In addition, lack of recognising that the patient is suffering from ALI/ARDS was reported. Another study identified in addition, lack of knowledge as a barrier to provide lung protective ventilation. For the lack of knowledge, implementing a DSS at the bedside could be method to bring the guideline into clinical use. To address the other barriers just introducing a DSS can not be expected to be sufficient, and different interventions should be used these including effective leaders and a process of feedback and education [22,24,87]. A barrier towards implementation of a guideline for ventilator settings may also be a lack of

consensus toward optimal ventilator settings, as this being identified in the evaluation of the model of preference. To address this, a process of clarifying consensus may be necessary with this including a group of experts either in the department, which is to implement guidelines, or on a more superior level such as an expert panel [88].

In the process of developing a model based decision support system this PhD project has been addressing the first steps, description and retrospective evaluation. The DSS can be seen as a prototype only providing advice for three ventilator settings i.e. FiO_2, f and Vt, in controlled ventilation. In this context it has been considered preliminary to engage groups of clinical experts in the process of developing the model of clinical preference. However, prior to introducing the DSS clinically to perform prospective evaluation, it would be appropriate to identify the opinion of the experts in the department and aim at developing a consensus such that the penalty functions could be defined and scaled accordingly. In such a process, the physiological model could be tuned to represent an individual patient and then to perform "what if" question by simulating the outcome of different combinations of ventilator settings. Thereby it would be made explicit where a process towards reaching consensus is required. As illustrated by the results of the evaluation of the model of clinical preference, this could be required for tidal volume strategy in patients with normal compliance or for level of FiO_2. If consensus can be expressed in a set of patient cases including ventilator settings and outcomes, it has previously been shown that rescaling of penalty functions may be automated [70].

For the model of clinical preference, it should be recognised, that there also is patient groups where redefinition will be necessary. For example, in COPD patients penalty functions should reflect the situation where lower levels of oxygenation and higher CO_2 are accepted as normal for these patients. In addition, for patients with head trauma the penalty functions should reflect a tighter strategy towards normo-ventilaton to prevent increased intra-cranial due to high CO_2 values. The structure of the DSS would enable simple specifications of different sets of penalty functions.

5. Conclusion

In this thesis, the DSS INVENT has retrospectively been evaluated for the feasibility of the advice provided for three ventilator setting (FiO_2, Vt and f) in controlled mechanical ventilation. In addition, the model of clinical preference based on penalty functions in a decision theoretic approach has been evaluated. To set the scene for the evaluation the DSS has been presented, this including description of the structure, the physiological models, the model of clinical preference and the use of the system in three steps. The system has been shown able to describe patient state in uncomplicated post-operative CABG-patients, and through further development including a more complex model of gas-exchange, patients suffering from ALI and ARDS. Analysis has shown that the system's advice is relatively insensitive to variation in CO and as such, the system can be used where a PAC is not available. When tuned to the individual patient the system provides parameter values describing pulmonary shunt and V/Q-mismatch, which offers a deeper understanding of the patients' physiology, a potential aid in monitoring the effect of different therapeutic interventions such as a recruitment manoeuvre. Tuning of the system to the individual means that advice is based on the individual's physiology. For example, in situations of high CO_2 production the risk of acidosis is increased and high ventilatory volumes may be justified. In retrospective evaluation of the DSS it has been shown that reasonable advice can be provided for f, Vt and FiO_2 in a homogeneous, well-monitored post-operative CABG patients and in more complex, severely ill ALI and ARDS patient. In the evaluation of the model of clinical preference, the DSS was evaluated comparably to how clinical experts evaluate each other, and a lack of consensus as to preference of ventilator settings was identified. Prior to clinical prospective evaluation of the DSS, a process of reaching consensus toward ventilator settings will be required and the penalty functions must be defined and scaled accordingly.

Acknowledgement

I wish to express my sincere gratitude to:

Stephen E. Rees, my supervisor, for his friendship, positive attitude, patience and valuable guidance through the PhD project.

Per Thorgaard, co-supervisor and head of 1th Department of Anaesthesia and Intensive Care for setting the frame making this PhD possible and for his enthusiastic support.

Steen Andreassen, co-supervisor, for inspiration and sharing his insight especially into the process of evaluating decision support systems.

Dan S Karbing, for his most appreciated friendship, invaluable contribution to the modelling process and our discussion of ours projects.

Bodel S. Rasmussen for making data available for the first steps in the process of evaluating INVENT.

Søren Kjærgaard for his friendship and support.

All my other colleagues at the Department of Anaesthesia and Intensive Care North for their support and patience.

And, most of all, my husband Per and my children Frederik, Viktor, Martine, Carl August and Ludvig for their understanding and support, and for always being there.

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Summary

In intensive care, mechanical ventilation is a central supportive therapy. Setting the ventilator appropriately can be difficult but nonetheless important as inappropriate settings have shown to increase patient mortality. To aid in the process of mechanical ventilation decision support systems has been developed. This PhD thesis has addressed the feasibility and retrospective clinical evaluation of a decision support system based on physiological models and a model of clinical preference in a decision theoretic approach. This system can provide advice for three ventilator settings (FiO_2, Vt and f) in controlled mechanical ventilation.

To set the scene for the retrospective clinical evaluation the decision support system INVENT has been presented including a description of the structure, the physiological models describing gas-exchange and lung mechanics, and the model of clinical preference including penalty functions. In the retrospective clinical evaluation it has shown feasible for INVENT to describe patient state in uncomplicated CABG-patients, and through implementation of a more complex model of gas-exchange, patients suffering from ALI and ARDS. Analysis has shown that the advice for ventilator settings is relatively insensitive to variation in CO and as such, the system does not require monitoring using PAC. As INVENT is tuned to the individual patient, it provides parameter values describing pulmonary shunt and V/Q- mismatch which may help an understanding of the patient's physiology, and in addition the advice provided for ventilator settings is based on the specific patients physiology.

Retrospective evaluation of INVENT in homogenous, well-monitored post-operative CABG-patients has shown that reasonable advice can be provided for f, Vt and FiO_2. The advice considered reasonable as it was consistent with ventilator settings used in clinical practice and with maintaining sufficient oxygenation while reducing risk of oxygen toxicity, normalising pH and achieving low values of PIP. In severely ill ALI and ARDS patients retrospective evaluation of INVENT has shown that the advice provided can be considered clinically rational and reasonable. Clinically rational as high FiO_2

and minute ventilation were advised in patients with oxygenation problems, acidosis and low PIP, respectively; and clinically reasonable as the advice and the model simulated outcomes were consistent with recommendations from ARDSNet.

INVENT combines the physiological models and the model of clinical preference based on penalty functions in a decision theoretic approach. The penalty functions enables INVENT's advice to be both explicit and transparent with trade-offs quantified numerically, and easily understood via simulation of "what-if" question using the physiological models.

As INVENT's advice appeared reasonable in the two patient groups it could be assumed that the penalty functions is an adequate representation of clinical opinion. Such an assumption is however, not consistent with the results of the evaluation of the model of clinical preference, as this clearly illustrated a lack of consensus toward a single reasonable clinical opinion. This evaluation provided little information to weather the model of clinical preference can be used in clinical practice to represent the opinion of a group of clinicians This might raise the question as to the appropriateness of no consensus towards reasonable ventilator settings. In a process of standardisation through reaching consensus INVENT may be a useful tool, as the physiological models allow different clinicians, to simulate how the same patient would behave in response to changing ventilator settings and discuss opinion as to both settings and outcomes in particular patient cases.

In conclusion, in retrospective clinical evaluation of the DSS has shown that reasonable advice is provided for f, Vt and FiO_2 in homogeneous, well-monitored post-operative CABG patients and in more complex, severely ill ALI and ARDS patient. In the evaluation of the model of clinical preference, the DSS was evaluated comparable to how clinical experts evaluate each other, and a lack of consensus as to preference of ventilator settings was identified. Prior to clinical prospective evaluation of the DSS, a process of reaching consensus toward ventilator settings will be required and the penalty functions must be defined and scaled accordingly.

Danish Summary

Respirator terapi må betragtes som en kerneydelse i intensiv terapi. Valg af passende respirator indstillinger kan ofte betragtes som vanskeligt men afgørende, idet uhensigtsmæssige respirator indstillinger har vist sig at øge patient mortalitet. Med henblik på at understøtte processen omkring valg af respirator indstillinger er der udviklet beslutningsstøttesystemer. I denne PhD-afhandling evalueres beslutningstøttesystemet INVENT baseret på fysiologiske modeller og en model af klinisk præference baseret på beslutningsteori. Beslutningsstøttesystem kan på basis klinisk rutine monitorering rådgive for tre respirator indstillinger (FiO_2, Vt and f) for kontrolleret mekanisk ventilation.

at Beslutningsstøttesystemet INVENT er blevet præsenteret, dette inkluderende en beskrivelse af systemets struktur, de fysiologiske modeller som beskriver lunge gas udveksling og mekanik, og modellen af klinisk præference som baseres på strafpointfunktioner, her penalty funktioner. Det er vist at INVENT kan give en beskrivelse af patient status hos ukomplicerede post-operative CABG-patienter, og i mere komplicerede patienter med ALI og ARDS. Rådende for respirator indstillinger har ved analyse vist sig at være relativt ufølsomt for variationer i CO, således kræver INVENT ikke at patienter monitoreres med PAC. INVENT bliver tilpasset hver enkelte patient og kan således give værdier for parameter, som beskriver lunge shunt and V/Q-mismatch, og giver således måske en bedre forståelse af patientens fysiologi, og samt gør rådet for respirator indstillinger patient specifikt.

INVENT kombinerer de fysiologiske modeller med modellen af klinisk præference baseret på penalty funktioner i en beslutningsteoretisk tilgang. Disse penalty funktioner medfører at INVENT's råd er eksplicit og gennemskueligt, da kompromiser beregnes numerisk og nemt kan forstås gennem simulering af "hvad hvis" spørgsmål vha. de fysiologiske modeller.

Retrospektiv evaluering af INVENT i homogene intensivt monitorerede post-operative CABG- patienter har vist at rimelige råd gives for f, Vt og FiO_2. Rådet betragtedes som rimeligt, idet det er konsistent med respirator

indstillinger anvendt i klinisk praksis, samt med vedligeholdelse af oxygenering samtidig med at risiko for ilttoksisitet blev reduceret, og normalisering af pH under anvendelse af lave PIP værdier. Ligeledes for kritisk syge patienter med ALI og ARDS har retrospektiv evaluering vist, at INVENT's råd er klinisk rationelt og rimeligt. Klinisk rationelt da høj FiO_2 og minut ventilation blev anbefalet til patienter med henholdsvis oxygenerings problemer, acidose og lavt PIP, og klinisk rimeligt da rådene og de model simulerede outcome var konsistente med rekommandationerne fra ARDSNet.

Da INVENT's råd er rimelige i de to patient grupper kunne det antages at penalty funktionerne er en adækvat repræsentation af klinisk præference. Denne antagelse er imidlertid ikke umiddelbart forenelig med resultatet af evalueringen af modellen for klinisk præference. Denne viser klart, at der ikke er konsensus omkring en enkelt repræsentation af klinisk mening. Denne evaluering giver således ringe information om modellen for klinisk præference kan repræsentere en gruppe af klinikeres præference for respirator indstillinger. Resultatet giver anledning til at rejse spørgsmålet om det er hensigtsmæssigt at der ikke eksisterer konsensus i relation til rimelig respirator indstilling. I en diskussion af dette og i en eventuel standardiserings proces kunne INVENT understøtte processen, da de fysiologiske modeller tillader forskellige klinikere at simulering, hvordan den samme patient ville reagere på ændringer i respirator indstillinger.

Det kan konkluderes, at den retrospektive kliniske evaluering har vist at beslutningsstøtte system INVENT kan rådgive hensigtsmæssigt om respirator indstillinger for fraktionen af inspiratorisk ilt, respirations frekvens og tidal volumen for homogene vel-monitorerede stabile post-operative CABG patienter, og for mere komplekse kritisk syge ALI /ARDS patienter. I evalueringen af modellen for klinisk præference blev INVENT's råd evalueret sammenligneligt med, hvorledes de kliniske eksperter evaluerede hinanden, og en manglende konsensus omkring passende respirator indstillinger blev identificeret. Således må der forud for prospektiv evaluering af INVENT forudsættes en konsensus proces og penalty funktionerne må kalibreres i henhold til denne.