Physiological models of gas exchange in decision support of mechanical ventilation

prospective evaluation in an intensive care unit

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Prospective evaluation in an intensive care unit

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Physiological models of gas exchange in decision support of mechanical ventilation – prospective evaluation in an intensive care unit

Abstract of thesis defended 27 November 2009

Introduction: Management of mechanical ventilation is a complex process of finding the right balance between conflicting goals, where clinicians must make timely decisions in unfavorable circumstances. Minimal models of pulmonary gas exchange may be used at the bedside in the intensive care unit to help in this process providing a deeper understanding of the patient's gas exchange status. The aim of this PhD project was to build and evaluate minimal models of gas exchange, and prospectively evaluate a minimal model-based decision support system.

Methods: Three retrospective studies were performed using data from various patient types including intensive care patients: comparing a hypoxemia index and model of O_2 gas exchange available in clinical practice with a two parameter minimal model; evaluating a decision support system for suggestions of inspired O_2 fraction; and investigating three minimal models of varying complexity for their ability to describe gas exchange of both O_2 and CO_2. A prospective study was performed in an intensive care unit to compare decision support system suggestions of inspired O_2 and resulting oxygenation with those selected by attending clinicians.

Results: The often used hypoxemia index, PaO_2/FiO_2 ratio, varies significantly with changes in inspired O_2, a common change in therapy. The clinically available shunt only model of gas exchange can not accurately describe this variation, a two parameter minimal model describing shunt and ventilation-perfusion mismatch can. The decision support system provides appropriate suggestions of inspired O_2 fraction retrospectively, and prospectively. A three parameter minimal modeling complexity is necessary for an accurate description of gas exchange of both O_2 and CO_2.

Conclusions: A minimal model-based decision support system can be used to provide a deeper understanding of the individual patient's gas exchange status, and to provide appropriate suggestions on inspired O_2 fraction freeing the focus of clinicians for more challenging therapies.

List of Papers

The thesis is based on the four listed papers, which will be referred to in the text by their corresponding roman numerals:

I Karbing DS, Kjærgaard S, Smith BW, Espersen K, Allerød C, Andreassen S , Rees SE.
Variation in the PaO_2/FiO_2 ratio with FiO_2: mathematical and experimental description, and clinical relevance.
Critical Care 2007, **11:**R118.

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Critical Care 2007; 11(6):182.
Critical Care 2008; 12(1):407; Author reply 407.

II Karbing DS, Kjærgaard S, Smith BW, Allerød C, Espersen K, Andreassen S, Rees SE.
Decision support of inspired oxygen fraction using a model of oxygen transport.
IFAC PapersOnLine, Proceedings of the 2008 Congress of the International Federation of Automatic Control, Seoul, Korea, July 6 – 11, Vol. 17(1) (DOI: 10.3182/20080706-5-KR-1001.2130)

III Karbing DS, Allerød C, Thorgaard P, Carius A, Frilev L, Andreassen S, Kjærgaard S, Rees SE.
Prospective evaluation of a decision support system for setting inspired oxygen in intensive care patients.
In press. Journal of Critical Care (DOI: 10.1016/j.jcrc.2009.12.013)

IV Karbing DS, Kjærgaard S, Andreassen S, Espersen K, Rees SE.
The minimal model approach to quantification of pulmonary gas exchange of oxygen and carbon dioxide.
In preparation.

Contents

Abbreviations and symbols

In the thesis, most measurements and model variables are written as a main symbol followed by a modifier and substance, e.g. $PaCO_2$ for partial pressure of carbon dioxide in arterial blood, or with no specific substance, e.g. $\dot{V}A$ for alveolar ventilation. Hemoglobins are not defined for specific blood components and are specified without a modifier, e.g. CHb for Hemoglobin concentration in blood.

Main symbols

F	Gas fraction	Q	Cardiac output
P	Gas pressure	$\dot{V}$	Ventilation
C	Concentration	V	Volume
S	Saturation		

Modifiers

A	Alveolar	Dana	Anatomical dead space
i	Inspired	a	Arterial
et	End-tidal	mv	Mixed venous
c	Capillary	p	Pulse oximetry
t	Tidal	m	Model predicted

Substance

O_2	Oxygen	CO_2	Carbon dioxide
Hb	Hemoglobin	MetHb	Met-hemoglobin
COHb	Carboxy-hemoglobin		

Other abbreviations and symbols

ΔPO_2	O_2 pressure drop from alveolar air to lung-capillary blood	$\dot{V}A/Q$	Alveolar ventilation/perfusion ratio
DSS	Decision support system	DPG	2,3-diphosphoglycerate
PEEP	Positive end-expiratory pressure	VILI	Ventilator Induced Lung Injury
ICU	Intensive Care Unit	MIGET	Multiple inert gas elimination technique
f	Respiratory frequency		

... modelling is assuming a more prominent role in mainstream anaesthesia and critical care research, becoming an accepted methodology and an ever-more useful part of the research process.

... Modelling runs through all of our endeavours, and we stand to benefit hugely by becoming acquainted with this powerful device.

J. G. Hardman and J. J. Ross
Editorial in British Journal of Anaesthesia 2006
Vol 97, pages 589-92

1. Clinical and technical background of the project

1.1 Introduction

Mechanical ventilation is a life-sustaining therapy used to secure sufficient oxygenation and carbon dioxide elimination and spare patients' energy allowing them to cope with underlying diseases and recover from surgery or trauma. Managing mechanical ventilator settings for ventilator therapy of the common postoperative patient is generally a simple task mainly comprised of weaning the patient from ventilator support, i.e. stepwise reduction in ventilator support until the patient alone is driving ventilation. However, in critically ill patients presenting in the intensive care unit (ICU), with failure of one or more organ systems often including the lungs, managing mechanical ventilation is a complex task. In these patients, selecting the appropriate ventilator settings can be considered as a search for the optimal compromise of conflicting goals. Such a search would preferably be performed based on a good understanding of the patient's lung function. However, this is often difficult using the vast number of relatively simple measurements currently available in the ICU. Mathematical models of pulmonary gas exchange may be used to integrate simple measurements and provide a deeper understanding of the patient's underlying physiology and pathophysiology. Implementing such models in decision support systems (DSSs) to calculate suggestions on therapy and provide physiological understanding may provide a valuable tool for clinicians, when deciding on appropriate therapy.

To illustrate the need for DSSs in mechanical ventilation, section 1.2 will present the clinical background of the project. The syndromes acute lung injury and acute respiratory distress syndrome are introduced. Ventilator induced lung injury (VILI) will be presented constituting the background of recent approaches to mechanical ventilation, termed lung protective ventilator strategies. Recent studies on ventilator strategies will also be introduced illustrating the lack of consensus on how to properly mechanically ventilate patients with severe lung disorders. In section 1.3 the literature on decision support systems is reviewed covering rule-based systems representing the most prevalent type of DSS, and model-based DSS. The focus of this PhD is decision support of mechanical ventilation using models of pulmonary gas exchange. Model-

based DSSs require physiological models which can predict the response of the individual patient to changes in therapy and preferably also provide the clinician with a deeper understanding of the lung status of the patient. Section 1.4 contains a review of currently available measurements and models of pulmonary gas exchange in clinical practice, the reference technique for measurement of pulmonary gas exchange and finally 'minimal' models of gas exchange, which represent compromises between the oversimplified models in clinical practice and the complex techniques used in the pulmonary laboratory. The scientific and clinical questions which have formed the aims of this PhD project are stated in section 1.5.

1.2 Managing mechanical ventilation in the ICU

Acute lung injury and the acute respiratory distress syndrome

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are syndromes of inflammation and increased permeability with significantly impaired lung function, the only difference between the syndromes being a more severe degree of hypoxemia in ARDS patients.

In 1994, Bernard and co-authors published a now generally accepted definition of the syndromes [1]:

- Acute onset
- Hypoxemia
    - ALI: $PaO_2/FiO_2 \leq 300$ mm Hg (40 kPa) regardless of PEEP level
    - ARDS: $PaO_2/FiO_2 \leq 200$ mm Hg (27 kPa) regardless of PEEP level
- Bilateral infiltrates seen on frontal chest radiograph
- Pulmonary artery wedge pressure ≤ 18 mm Hg or no clinical evidence of left atrial hypertension

The incidence of ALI and ARDS in Denmark were reported in 2000 to be 17.8 and 14.6 patients per 100000/year, respectively [2], with 90-day mortalities being 47.3 % and 46.5 %, respectively [2]. A later European study reported that 7 % of all patients admitted to an ICU and 15 % of patients mechanically ventilated for at least 24 hours had or developed ALI/ARDS [3]. This study reported hospital mortalities in ALI and ARDS patients of 32.7 % and 57.9 %, respectively.

The lung damage seen in lungs of patients with ALI/ARDS is heterogeneously distributed with alveolar collapse and alveolar over-distension seen in different regions of the lungs [4]. Collapse is mostly reported to occur in dependent regions whilst over-distension is seen in the non-dependent regions, often referred to as the baby-lung of ALI/ARDS [4,5]. The severity and spread of lung damage increases the need for aggressive ventilator support such as high levels of inspired oxygen (FiO_2) and high pressures and volumes but at the same time also increases the risk for ventilator induced lung injury (VILI). For example, increases in pressure and volume may act to open collapsed alveoli improving gas exchange in some regions whilst further over-distending alveoli in other lung regions causing lung damage.

Ventilator induced lung injury

The fact that mechanical ventilation may cause damage to the patient's lungs is not new and was discussed as early as in the 1700s [6]. However, over the last decades the topic has received increasing attention with the realization that other damaging mechanisms exist besides air leaks due to rupture of the airspace wall caused by high pressures (barotrauma) [7,8]. Studies of lungs from animals and patients who have undergone ventilator therapy with large pressures and volumes have shown lung tissue damage such as interstitial fibrosis, hyaline membranes and alveolar edema [8,9].

In addition, the major cause of death of ALI/ARDS patients has been found not to be hypoxemia but multiple organ failure [3,10]. Several authors have suggested that VILI has an important role in the pathology of multiple system organ failure due to hypoxia, release of inflammatory mediators (biotrauma), and spillover of these mediators and bacteria to the blood due to increased alveolar and microvascular permeability [11-12].

Biotrauma has been shown in relation to injurious mechanical ventilation in both animals and patients [8, 13-15] but not all results have been consistent [16]. Two mechanisms, termed volutrauma and atelectrauma, have been suggested as causes of tissue damage, biotrauma and increased alveolar and microvascular permeability. Overdistension of lung tissue due to high volumes and/or pressures (volutrauma) occurs, in particular, in the baby-lung of ARDS where tidal volumes considered

normal in healthy lungs are deleterious [5]. Repeated recruitment and de-recruitment of atelectic lung regions (atelectrauma) has been suggested to cause stress and strain in the junctions between adjacent alveoli [8,17]. The physical stress and strain involved in volutrauma and atelectrauma may lead to epithelial damage and increased alveolar and microvascular permeability causing pulmonary edema [8]. Volutrauma and atelectrauma may also impair the function of pulmonary surfactant [18]. Surfactant is a chemical compound which acts on the air/water interface inside the alveolar epithelium to reduce surface tension lowering work of breathing, maintaining fluid balance across the alveolar membrane and preventing alveolar collapse [18].

High fractions of oxygen in the inspired air (FiO_2) can also affect lung status leading to gas-exchange impairment or tissue damage. High levels of FiO_2 can cause atelectasis in regions with low ventilation/perfusion ratios [19-21] and cause toxic effects [22-23].

Lung-protective ventilator strategies

The role of mechanical ventilation as a major cause of patient mortality has spurred numerous experimental investigations and clinical trials addressing how to properly manage mechanical ventilation, in particular in ALI/ARDS patients. In the following, some of the major studies within lung-protective ventilation are described.

In 1998, Amato and coworkers described a statistically significant improvement in 28-day mortality in 53 ARDS patients by using a strategy consisting of: recruitment maneuvers i.e. short periods of large pressures to open atelectic lung regions; positive end expiratory pressure (PEEP) to keep recruited alveoli open; and small tidal volumes to reduce lung tissue stress [24]. After 28 days the mortality of the lung protective group was 38 % compared to 71 % in the conventionally treated group. However, several studies with similar strategies and number of patients did not find significant differences in mortality between low and high tidal volumes [25-27].

A large multicenter study conducted by the Acute Respiratory Distress Syndrome Network (ARDSNet) followed the trial by Amato et al. comparing the use of small and large tidal volumes [28]. This study showed that a strategy comprising tidal volumes small (Vt = 6 ml/kg) in comparison to previously common tidal volumes and

peak inspiratory pressures less than 30 cmH_2O resulted in improved mortality compared to large tidal volumes (Vt = 12 ml/kg) and peak inspiratory pressures less than 50 cmH_2O.

A later study conducted by the ARDSNet investigated the use of low versus high PEEP, maintaining a Vt of 6 ml/kg in both groups [29]. The study did not find any significant difference in mortality between the two groups. However, later analysis has indicated that this study might not have had large enough differences in PEEP levels between the two groups to demonstrate a significant difference in mortality [18].

Larger differences between PEEP levels in two patient groups (13.4 ±2.6 cmH_2O in 53 patients vs. 9.8 ± 2.8 cmH_2O in 50 patients) were reported in a recent study to produce significant improvement in mortality [30]. However, the two groups were ventilated with different tidal volumes preventing the authors from drawing conclusions on the importance of PEEP levels on mortality [30]. In addition, two recently published multicenter trials compared two groups with equal low tidal volumes but with lower and higher PEEP levels [31,32]. Neither of these two studies could demonstrate significant differences in mortality between the studied patient groups.

The focus of current ventilator strategies is on preventing VILI by lowering volumes and pressures. However, FiO_2 should not be increased indiscriminately to secure oxygenation [19-23], and several authors have pointed out that low tidal volumes may lead to low ventilation/perfusion ($\dot{V}A/Q$) regions in the lungs, which limits gas exchange and are highly susceptible to adsorption atelectasis due to hyperoxia [33,34]. Although not the focus of recent debate, the vast majority of clinical trials have included limitation of FiO_2 either directly or through goals for oxygenation in their ventilator strategies [15, 24-29, 31,32].

Whilst there is a general consensus that the lungs should be ventilated with caution, there is also a general consensus that the understanding of the different types of lung damage and the mechanisms involved is not complete [16-18,33-35]. Furthermore the

varying results from clinical trials indicate that the perfect ventilation strategy, if there is such a thing, has yet to be found. It has been speculated, that the heterogeneity of ALI/ARDS patients requires that every patient should be treated on an individual basis [17], which is supported by recent clinical studies [36,37]

This leaves intensive care clinicians with a far from straightforward task, which needs to be performed in a timely manner, based on interpretation of large amounts of data. The increasing complexity and available options on modern ventilators do not help to alleviate the problem. These circumstances work against human nature. The human brain can process a limited amount of information when making decisions [38], which combined with the stressful environment of the ICU have been suggested as augmenting factors for errors committed by health care professionals in the ICU [39, 40]. These points illustrate that DSS for mechanical ventilation may be beneficial.

1.3 Decision support systems for mechanical ventilation

Decision support systems (DSSs) may be categorized with regards to several aspects: open or closed loop; approach to data integration and analysis; approach to decisions, e.g. rule-based, utility theory, etc.; and the settings optimized by the system. In the following, the literature is reviewed categorizing published DSS for mechanical ventilation into rule-based systems and model-based systems. Rule-based systems will refer to systems that are mimicking experts in the field or clinical guidelines performing data integration and analysis using the clinical measurements directly without physiological models.

Rule-based systems

The vast majority of developed DSS for ventilator management have been rule-based systems [41-63]. These systems have often been developed for specific subproblems of ventilator management such as weaning patients from mechanical ventilation [49].

Figure 1 shows the general overall structure of such systems. Rule-based systems typically include 4 overall components: data input; data integration and analysis; rule base; and decision control (often also called inference engine). The interaction and integration of these components may vary from system to system. Data input can consist of ventilator settings, lung mechanic measurements, gas exchange

measurements, metabolic measurements, hemodynamic measurements and patient characteristics such as height, diagnosis etc. These data may be automatically retrieved from the ventilator and monitoring devices, or typed in manually by the clinician, or both. The role of the data integration and analysis component varies from system to system but may be comprised of tasks such as data validation and classification e.g. removal of noise, and temporal data analysis. The rule base comprises the built-in rules of the system, e.g. IF-THEN-ELSE descriptions linking patient physiological data with system response. The decision control component selects the advice to provide to the clinician.

If the DSS is an open-loop system the clinician manually sets the ventilator settings according to the suggestions provided by the DSS. In a closed-loop system the DSS automatically adjusts the ventilator settings. Irrespectively, rule-based systems have in common that they are black-box systems, i.e. the clinician is not aware of the considerations involved in the suggestions provided by the systems.

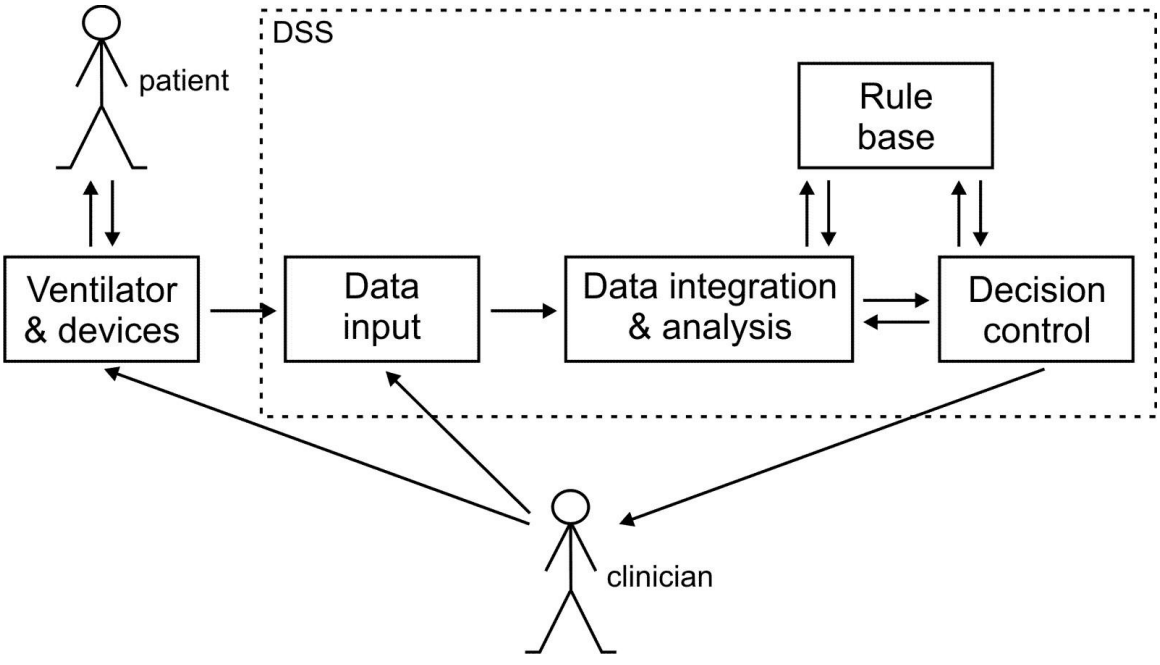

Figure 1: The general structure of a rule-based decision support system for ventilator management.

Strict rule-based systems i.e. comprised of IF-THEN-ELSE rules are predominating [41-58]. In the simplest form these are relatively easy to implement and constitute

electronic versions of paper based clinical guidelines [e.g. 45-48]. Almost all published DSS based on this simple structure have been prospectively evaluated [41-53]. Two of these studies have been large multicenter randomized trials [48, 53]. The study reported by East et al. investigated a clinical guideline for managing ARDS patients, and although the implemented clinical guideline did not result in statistically significant improvement in mortality, the study demonstrated the feasibility of implementing a DSS across several institutions [48]. The study by Lellouche et al. compared weaning of patients using a closed-loop DSS (GANESH) [49] with weaning using written clinical guidelines [53]. The patient group weaned using GANESH had lower duration of weaning, shorter duration of mechanical ventilation and shorter ICU stay [53]. GANESH has also been implemented as part of a commercial system, termed SmartCare™/PS by Dräger Medical [64].

Adaptive support ventilation (ASV) is another commercially available closed loop DSS, implemented in Hamilton ventilators [65]. When using ASV the clinician defines a desired minute volume and the system automatically adjusts respiratory frequency, tidal volume and inspiratory pressure and switches between support and control behavior using rules according to measurements of the patient's lung mechanics [65]. Several studies have been performed using ASV, for example a multicenter study comparing ASV with controlled ventilator modes in patients with acute respiratory failure [66]. The study showed that ASV could maintain similar $PaCO_2$ as clinicians but with lower peak airway pressures.

In addition to SmartCare™ and ASV several advanced ventilator modes have been developed which have elements in common with DSS. Most notable are proportional assist ventilation (PAV), and neurally adjusted ventilatory assistance (NAVA) which can be considered advanced versions of the pressure support mode. These systems determine the level of pressure support using a gain factor adjusted by the clinician combined with either measured inspiratory flow (PAV) or the electromyographic activity from the diaphragm (NAVA) [67].

Different research groups have taken alternative approaches to capture the heuristics of critical care experts [59-63]. These approaches include knowledge bases using automated knowledge acquisition [59], and fuzzy logic for temporal data

classification [60, 63], to derive the rule base [62], and to mimic human decision-making [61]. One of these systems have been implemented and prospectively evaluated in 7 neonates showing agreement between clinicians and provided advice in more than 90% of cases [63].

The black-box approach shared by all the presented rule-based DSS is also one of the major weaknesses of these systems, as they do not provide the clinician with a deeper understanding of the individual patient's status. If changes in settings alter the status of the patients this may require reevaluations leading to new changes. As such, the rule-based systems may require a trial and error approach. Model-based DSS may solve both of these problems. Parameters of physiological models may provide a deeper physiological understanding of the patient. In addition, once model parameters have been tuned to fit the individual patient data, models can predict patient response to changes in ventilator settings allowing the clinician quick evaluation of therapy changes, thereby eliminating the need for the trial and error approach [68].

Model-based decision support in ventilator management

Figure 2 shows the overall general structure of model-based DSS in ventilator management. Five overall components are generally included: data input; physiological models; parameter identification; model prediction; and decision control. The data input component is conceptually identical to that of the rule-based systems. The physiological model component constitutes the physiological models used in a model-based DSS such as models of pulmonary gas exchange. Parameter estimation often constitutes measurement of patient response to small variations in therapy to allow tuning of model parameters to fit the physiological models to the individual patient. This process can be manual with the system interacting with the user during the process or it can be automated. Parameter estimation will often encompass the data integration in the system. Once fitted to patient data the models can be used to simulate patient response to changes in therapy, e.g. changes in oxygenation upon changes in inspired oxygen fraction. This can involve the clinician, by letting the clinician test different changes in settings without involving the patient or it can be done by the DSS to calculate optimal therapy. This can be performed by a decision control component using mathematical functions associating different strategies with corresponding utilities, i.e. models of clinical preferences. Hybrid

systems have also been developed where physiological models are combined with a rule base to decide suggestions on therapy.

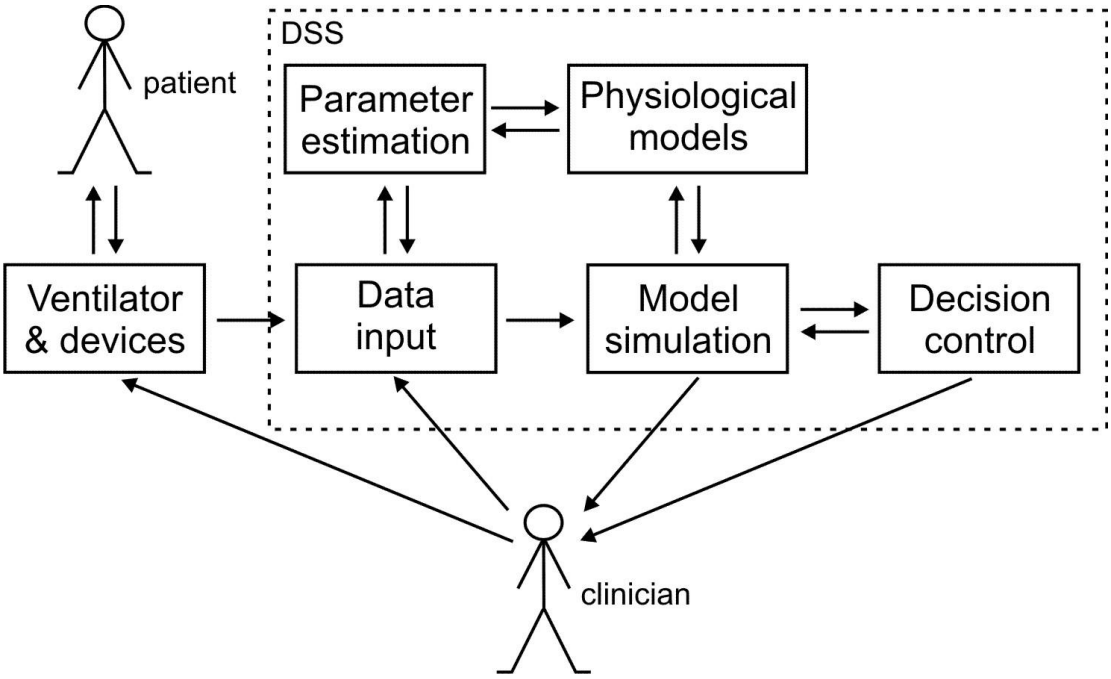

Figure 2: General structure of model-based decision support systems for ventilator management.

Model-based DSSs may solve two problems, i.e. providing a deeper understanding of patient physiology and preventing trial and error approach to ventilator management. However, they may also introduce two overall limitations. When physiological models are integrated into the calculation of new advice, model-based DSS depend on the implemented models to accurately predict patient response to changes in ventilator settings. In addition, in order to allow patient specific predictions, the model parameters must be tuned to fit patient specific data before suggestions on therapy can be calculated, and this may be a time-demanding process. These limitations have been dealt with in different ways by the different model-based DSS [69-74].

The first reported DSS using physiological models was the open-loop system OPTPROG [69]. OPTPROG found the combination of respiratory frequency (f), tidal volume (Vt) and PEEP which resulted in the minimal peak respiratory power (PRP), which was defined as an index of lung trauma. The system also maintained PaO_2 and $PaCO_2$ within limits defined by a clinician. OPTPROG was prospectively evaluated in 5 patients with various pulmonary diseases and 7 post operative coronary artery bypass graft patients showing that the system was able to minimize PRP whilst

maintaining adequate PaO_2 and $PaCO_2$ values [69, 70]. However, OPTPROG had a couple of significant limitations. OPTPROG was based on linear programming, and the model parameters had no physiological interpretation [68]. As such, the system did not provide clinicians with a deeper physiological understanding of the patient. In addition, estimation of model parameters required a time-demanding experiment taking approximately one hour involving frequent sampling of arterial blood beyond that of routine clinical practice [68].

The VentPlan system [71] used a model of pulmonary gas exchange to provide open-loop decision support of FiO_2, Vt and f. The implemented model was a classical three compartment model with model parameters having physiological interpretations [75]. The model includes two parameters: a shunt parameter which quantifies the fraction of pulmonary perfusion not reaching ventilated alveoli; and a parameter describing the amount of physiological dead space, i.e. the amount of ventilation not participating in gas exchange. Parameter estimation was performed as a combination of a Bayesian belief network and patient specific measurements [71]. The belief network was implemented to enable parameter estimation in cases when measurement data were insufficient to allow a unique numerical solution when estimating model parameters. Advice was calculated based on a combination of model simulations and utility theory [76], using penalty functions to model clinical preferences. VentPlan was retrospectively evaluated using data from 10 ICU patients indicating potential of the system [71]. However, to the best of my knowledge, VentPlan development stopped before any prospective evaluation could be performed.

The Sheffield Intelligent Ventilator Advisor (SIVA) uses a physiological model describing the same factors as that of VentPlan, i.e. shunt and physiological dead space [72]. SIVA uses the ratio between the alveolar-arterial oxygen difference to PaO_2 ($PA\text{-}aO_2$ / PaO_2) as an input to an Adaptive-Network-based Fuzzy-Inference System [62] to estimate the shunt parameter. To estimate the physiological dead space the system requires invasive measurement data using a pulmonary artery catheter and a numerical method, which the authors report has often convergence problems [72]. Alternatively physiological dead space could be estimated by the clinician. SIVA is a hybrid system and uses fuzzy rule-bases in combination with models to provide open-loop decision support of FiO_2, PEEP, inspiratory pressure (Pinsp) and f, although

without modeling the effect of PEEP. Evaluations of SIVA have so far been limited to simulation studies [72].

The open-loop system INVENT presented by Rees et al. uses a two parameter physiological model of gas exchange in combination with a model of the acid-base chemistry of blood as well as a simple model of lung mechanics [73]. The gas exchange model describes shunt and ventilation/perfusion mismatch, the two major factors affecting pulmonary gas exchange in patients with respiratory failure [77]. The parameters of the gas exchange model are estimated using a method comprised of varying inspired oxygen fraction in 4-6 steps and measuring the oxygen contents of the expired gas as well as pulse oximetry oxygen saturation (SpO_2), this process taking approximately 10-15 minutes [78]. The lung mechanics model requires input of PEEP and respiratory compliance and the blood model and the gas exchange model also require a single arterial blood gas measurement. The INVENT system provides advice on FiO_2, Vt and f using utility theory in the form of penalty functions combined with the three models [73]. At the beginning of this PhD project evaluations of the system had not been published.

The most recently introduced model-based DSS is the FLEX hybrid system, which can act both as an open-loop and a closed-loop system [74]. The approach of the FLEX system has similarities to the OPTPROG system with the implemented models being empirical by nature and mainly using model parameters without physiological interpretation. FLEX incorporates a large number of these simple models in combination with a rule base to calculate suggested levels of FiO_2, PEEP, f, I:E-ratio, PIP, and Vt as well as to wean patients [74]. In this process the system aims at minimizing the work of breathing using a modified version of an empirically derived equation [79]. The FLEX system does not require any parameter estimation procedures, but use readily available measurement data or parameters which are not fitted to the individual patient. So far, the system has been limited to retrospective evaluations, showing the suggestions of the system to be in general agreement with decisions taken by clinicians in ICU patients [74] and neonates [80].

1.4 Mathematical models of gas exchange

Measurements and models available in clinical practice

Several measurements are available in clinical practice which may provide some information regarding the gas exchange status of a patient. For oxygenation, measurement of arterial blood gases yields arterial partial pressure of O_2 (PaO_2) and arterial oxygen saturation (SaO_2). An arterial blood sample can also be analyzed to measure hemoglobins (Hb, MetHb and COhb) providing information regarding the oxygen carrying capacity of the blood. Hemoglobin concentration, PaO_2 and SaO_2 can also be used to calculate the total contents of O_2 in arterial blood. Oxygen concentrations and pressures can also be obtained from samples of central or mixed venous blood, yielding information regarding the use of oxygen by the organs and peripheral tissues, i.e. the general ischemic status of the body. Mixed and central venous blood samples, however, require catheters in the pulmonary artery or one of the larger veins (e.g. the internal jugular vein), respectively, and are not part of routine clinical care in all ICUs. These measurements need to be related to the ventilation and FiO_2 to be interpreted with regards to the lung status of the patient.

A range of oxygen tension based indices have been developed to aid in interpretation of oxygenation with regards to ventilator settings. The ratio between oxygen partial pressure in arterial blood to FiO_2 (PaO_2/FiO_2) is probably the most common index of hypoxemia, especially in clinical studies, and is part of the definition of ALI/ARDS. Another frequently used tension based index is the alveolar-arterial oxygen partial pressure difference ($PA\text{-}aO_2$) [81]. This index provides an estimate of the total drop in oxygen partial pressure through the pulmonary system. However, the index requires calculation of the alveolar partial pressure of oxygen (PAO_2) using the alveolar air equation requiring measurement of, or an assumed value of the respiratory quotient [81]. All these oxygenation measures and indices vary with one or more extrapulmonary factors such as ventilation and variation in FiO_2 which are common therapeutic interventions in mechanically ventilated patients and affect oxygenation but not the underlying physiology or pathophysiology of the patient [77,].

The standard method for evaluating pulmonary gas exchange of CO_2 is to measure the partial pressure of CO_2 in arterial blood ($PaCO_2$). In addition, capnography can be

used to evaluate the CO_2 contents in the expired gas in relation to either time or expired volume, although this is not commonly applied in the ICU [83]. Capnography allows measurement of end-tidal partial pressure or fraction of CO_2 ($PetCO_2$ or $FetCO_2$). When both $PetCO_2$ and $PaCO_2$ are available it is possible to calculate the $PetCO_2$-$PaCO_2$ difference which will increase with $\dot{V}A/Q$ mismatching and to a lesser degree venous admixture [84]. The anatomical and alveolar dead space volumes can also be calculated from the capnogram, the latter if a $PaCO_2$ measurement is available. Alternatively the physiological dead space can be calculated using Enghoff's modification of the Bohr equation [85] requiring $PaCO_2$ and measurement or calculation of the partial pressure of CO_2 in the mixed expired gas.

The current state of the art for quantifying pulmonary gas exchange in clinical practice is measurement of intrapulmonary shunt [81]. When measured at an FiO_2 less than 100% the value is termed venous admixture and describes the patient's pulmonary gas exchange abnormality as due to alveoli being perfused but not ventilated. It has been shown that the measurement of intrapulmonary shunt is inadequate to describe changes in oxygenation with variation in FiO_2, and that it is necessary to separate oxygenation problems into that caused by pulmonary shunt and that due to an alveolar-lung capillary drop in partial pressure of oxygen [86-88]. By measuring intrapulmonary shunt at FiO_2=100%, the intrapulmonary shunt can be measured without the effects of an alveolar-lung capillary drop in partial pressure of oxygen. However, inspiration of pure oxygen may cause absorption atelectasis thereby giving an overestimate of the true shunt value [19,89] and the method still gives no information regarding the presence of an alveolar-lung capillary drop in partial pressure of oxygen, such as due to $\dot{V}A/Q$ mismatching in the lungs.

The Multiple Inert Gas Elimination Technique

To appreciate the concept of minimal modeling and the compromises made, one should first look at the current reference technique for quantifying gas exchange in the pulmonary laboratory, which is the multiple inert gas elimination technique (MIGET) [90]. MIGET relies on measurement of retention and excretion of 6 inert gases sampling blood and expired gas data. MIGET uses a model of pulmonary gas exchange comprised of 50 compartments with different $\dot{V}A/Q$ relationships

accounting for an alveolar-lung capillary drop in partial pressure of oxygen. The model also includes shunt being the one extreme of the $\dot{V}A/Q$ range ($\dot{V}A/Q = 0$) and alveolar dead space being the other extreme ($\dot{V}A/Q = \infty$). This model is fitted to the retention and excretion data and the end result is reported as distributions of blood flow and ventilation across the compartments of the model.

Use of the MIGET technique in the pulmonary laboratory has contributed significantly to the current physiological understanding of pulmonary gas exchange in healthy subjects at different age [91], during anesthesia [92], in chronic obstructive pulmonary disease [89] and in patients with acute respiratory failure including ALI and ARDS [94]. MIGET studies have shown that lungs of ARDS patients are characterized by large fractions of shunt and in many patients there are lung regions with low $\dot{V}A/Q$ ratios and/or large fractions of ventilation going to alveolar dead space [94, 95]. The $\dot{V}A/Q$ distributions produced by MIGET have also been shown to describe the effects of various changes in therapy on pulmonary gas exchange [94]. In ALI/ARDS patients, for example, increases in PEEP as well as changes in posture from supine to prone have been shown to reduce shunt [95-98]. In addition, inspiration of 100 % O_2 has been shown to convert units with low $\dot{V}A/Q$ into shunt [94] possibly due to absorption atelectasis [19, 33-34].

The MIGET experimental procedure is highly complex and involves preparing and infusing the inert gases, sampling of blood and expired gases and analyzing these using gas chromatography [90], the technique is therefore inappropriate for routine clinical application.

Minimal modeling of pulmonary gas exchange

In the past 15 years a considerable effort has been made to formulate minimal models based on few model compartments and parameters which can be estimated from routine clinical data. As originally suggested by Riley et al [86,87] and King et al. [88] these models describe pulmonary gas exchange abnormalities as caused by intrapulmonary shunt combined with an alveolar-lung capillary drop in partial pressure of oxygen. The latter factor has been modeled either using one [99-101] or two compartments to describe $\dot{V}A/Q$ mismatch [78,102-104], one compartment with

diffusion limitation [102,105,106], or two compartments to describe both $\dot{V}A/Q$ mismatch and diffusion limitation [107,108]. These models are poor descriptions of physiology compared to the 50 compartment model of MIGET but significant improvements compared to measurement of intrapulmonary shunt or dead space volume alone.

Minimal models describing intrapulmonary shunt and an alveolar-lung capillary drop in partial pressure of oxygen have been shown to fit oxygenation data from normal subjects [99,103,106-108]; patients before [99,100,102,103], during [99-101] and after [99,100,102-104,106] major surgery; patients presenting in intensive care [103]; patients with chronic obstructive pulmonary disease (COPD) [107,108]; patients with incompensated heart failure studied before and after diuretic therapy [103]; and anesthetized mechanically ventilated dogs with acutely applied hypoxia or with induced intense small airway constriction in a rebreathing model of COPD [108].

The model describing intrapulmonary shunt and $\dot{V}A/Q$ mismatch presented by Kjærgaard et al. [102], which is the model used in INVENT, has also been shown to fit retention and excretion data comparable to MIGET in pigs before and after lung damage caused by oleic acid infusion [109]. Additionally the model presented by Vidal Melo and co-workers [107] has been shown to produce $\dot{V}A/Q$ distributions having positive correlations with MIGET $\dot{V}A/Q$ distributions in COPD patients and healthy subjects before and after exercise [108]. However, at present only a single model has been evaluated for its ability to describe gas transport of CO_2 [107,108].

1.5 Aims of the project

Management of mechanical ventilation in patients with severe lung disorders constitutes a process of balancing conflicting therapeutic goals. This is a complex task which clinicians in the ICU must perform based on numerous measurements in a stressful environment and with no clear evidence based strategies for several of the ventilator settings. Several DSSs have been developed to aid the clinician in this process. The majority of these systems have been rule-based DSSs, which may provide sound advice, but do not provide the clinician with a deeper understanding of the individual patient. Rule-based DSSs may also require a time demanding trial and

error approach as commonly used in clinical practice to find the appropriate settings. Model-based DSS may provide a more appropriate alternative. When models are tuned to fit patient data they may provide a deeper physiological understanding of the patient and predict patient responses to changes in therapy, thereby removing the need for trial and error. However, this requires models with parameters having physiological interpretation and which may be identified from routine clinical data. Measurements and models of pulmonary gas exchange currently available in clinical practice are oversimplified. In contrast the reference technique, the MIGET, is too complex to use in clinical practice. Minimal models have also been developed presenting compromises between feasibility and complexity. This PhD project has addressed the use of such minimal models to describe gas exchange in the ICU and their use in a DSS, through investigation of the following questions:

- How well do the current dominating oxygenation index (PaO_2/FiO_2 ratio) and gas exchange model (shunt model) used in clinical practice describe oxygenation in comparison with a two parameter minimal model of O_2 gas exchange describing both shunt and ventilation/perfusion mismatch? (Paper I)

- Can INVENT based on a two parameter model of gas exchange describing shunt and ventilation/perfusion mismatch combined with utility theory provide appropriate suggestions on FiO_2 when evaluated retrospectively in intensive care patients? (Paper II)

- Can INVENT manage FiO_2 in intensive care patients when evaluated prospectively? (Paper III)

- A model describing gas exchange of both O_2 and CO_2 is necessary for INVENT to provide suggestions of Vt and f in addition to FiO_2. What complexity is necessary for a minimal model representation of pulmonary gas exchange of both O_2 and CO_2? (Paper IV)

To address these questions technical methods were developed and refined. These tasks involved modeling of pulmonary gas exchange, methods for estimation of model

parameters, development of a version of INVENT used with a database system to provide suggestions on FiO_2. The technical solutions were similar between studies, but were adapted for the specific applications. The following chapter presents the technical methods used during the project, and the tailoring of the methods for the specific studies.

2. Gas exchange models and decision support system

This chapter describes the technical methods used to answer the four questions addressed in the PhD project. The project has evolved around minimal models of pulmonary gas exchange. Models of different complexity have been used in the studies, but all models have followed the same overall structure. The models are presented in section 2.1. Methods used for estimation of model parameters have been adapted to the individual studies depending on available measurement data and aims of the studies, the different approaches are explained in section 2.2. Section 2.3 presents the version of the DSS, INVENT, developed to provide suggestions on FiO_2. The system is integrated in a database system, ICARE, which is described briefly in section 2.4.

2.1 Minimal models of pulmonary gas exchange

All four studies were performed using physiological models with the same structure as the two parameter model originally presented by Kjærgaard et al [102]. These models are based on conservation of mass, continuous breathing and perfusion and assume steady state.

Figure 3 shows the overall structure shared by these models, indicating the model parameters in bold. In addition to the shown compartments all models used in the study have a serial dead space compartment. The model presented by Kjærgaard et al. has a shunt parameter (fs) describing the fraction of pulmonary perfusion not reaching ventilated alveoli. In addition the model has two ventilated and perfused compartments. The perfusion is locked at a specific distribution defined by the f2 parameter such that one parameter receives 90 % of non-shunted blood flow and the other 10 % (f2=0.9). Distribution of ventilation varies between the two compartments as defined by the fA2 parameter, such that a fA2 of 0.9 would result in optimal $\dot{V}A/Q$ matching, whereas fA2 less than 0.9 would signify $\dot{V}A/Q$ mismatching. This two-parameter model (fs and fA2) is used in all four studies, and is the model used in INVENT for predicting patient response to changes in FiO_2 in papers II and III.

In paper I, the two parameter model is compared with the ‘effective’ shunt model, which is a one-parameter model having a shunt compartment, and where non-shunted

blood flow goes to a ventilated compartment receiving all alveolar ventilation, i.e. with an optimal $\dot{V}A/Q$ matching. In paper IV, the 'effective' shunt model and the two-parameter model are compared with a three-parameter model where f2 is varied to fit patient data. Study IV investigated the use of the models in describing the pulmonary gas exchange of both O_2 and CO_2. A mathematical model of the acid base chemistry of blood [110] was therefore implemented in the models to also describe the storage of CO_2 in the blood. All model equations as well as the model of the acid-base chemistry of blood are presented in paper IV.

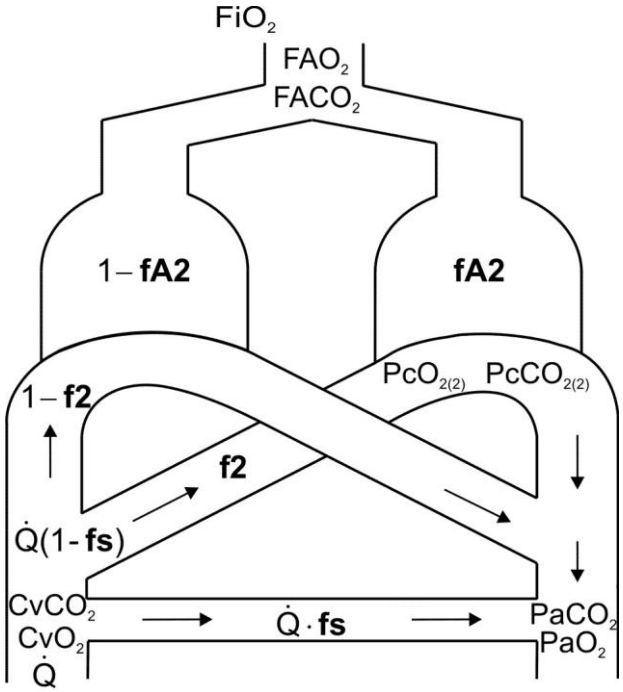

Figure 3: Structure of the physiological models used in the PhD project.

The parameters describing $\dot{V}A/Q$ mismatch can be transformed into a ΔPO_2 value, which quantifies the drop in partial pressure of oxygen from the alveoli to the capillaries leaving the lungs before the mixing with shunted venous blood. As such a ΔPO_2 value can be translated directly into the necessary extra pressure of O_2 at the mouth to alleviate oxygenation problems due to $\dot{V}A/Q$ mismatch, i.e. if ΔPO_2 = 10 kPa, approximately an extra 10 % oxygen is needed (FiO_2 = 0.31).

2.2 Estimation of model parameters

The effects of shunt and an alveolar to lung capillary drop in PO_2 can be separated by performing an experiment where FiO_2 is varied in steps and end-tidal O_2 and arterial

oxygenation are measured at each step after steady state is achieved. Rees et al introduced in 2002 an automated method where the steady state was monitored by looking at $FetO_2$ enabling a relatively fast experiment, taking approximately 10-15 minutes when 3-5 FiO_2 steps are taken [78]. Arterial oxygenation is estimated using pulse oximetry, which has been shown to produce accurate estimates of fs and fA2 model parameters in a variety of patient groups including intensive care patients [103].

To separate the effects of shunt and an alveolar to lung capillary drop in PO_2, the steps must be taken so that $FetO_2$-SpO_2 points are lying on either side of the characteristic shoulder of the $FetO_2$-SpO_2 curve. This normally requires variation in SpO_2 from 0.85-1. Shunt affects the $FetO_2$-SpO_2 curve in the vertical direction with increases in shunt depressing the curve. An alveolar to lung capillary drop in PO_2, i.e. as due to $\dot{V}A/Q$ mismatching, causes a horizontal shift in the curve with increase in $\dot{V}A/Q$ mismatching and larger PO_2 drop causing a shift to the right. Figure 4 shows an example of a dataset, where $FetO_2$-SpO_2 points lie appropriately, and the two-parameter model has been fitted to the data.

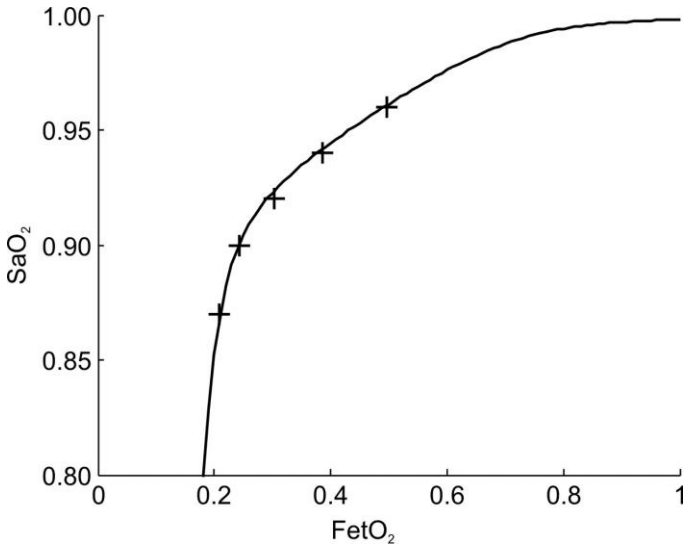

Figure 4: Example of resulting fit (solid line) from estimating model parameters of the two parameter gas exchange model, to fit measured $FetO_2$-SpO_2 data (+) using equation 1. Patient data are from an intensive care patient studied in papers I, II and IV.

Model parameters are estimated using numerical minimization methods finding the combination of model parameters resulting in the least weighted squared difference between simulated and measured values. Before the PhD project an error function had

been developed looking at the error in both the horizontal and vertical directions, as stated in equation 1.

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

WRSS is the weighted residual sum of squares, SmO_2 is the model predicted SaO_2, σ_{SpO2} is the standard deviation of SpO_2 and σ_{Horiz} is the standard deviation in the horizontal direction due to measurement uncertainty of $FetO_2$. σ_{Horiz} was calculated as the difference in SmO_2 caused by increasing measured $FetO_2$ by the standard deviation of $FetO_2$ measurement (σ_{FetO2}). σ_{SpO2} was set to 0.01 [103] and σ_{FetO2} was set to 0.005 [111]. Equation 1 was used to fit the two parameter model in figure 1.

In papers I and II, the measurement data included SaO_2 measurements at each level of FiO_2. SaO_2 was therefore used instead of SpO_2, to give the best possible model description of patient data. In study II this was performed in addition to fitting the model to SpO_2 data. The standard deviation of SaO_2 (σ_{SaO2}) was set to 0.005 [112].

Before study II, the error function was modified to use both SpO_2 and SaO_2, motivated by the fact that a single arterial blood gas measurement is necessary for the parameter estimation, so the inclusion of SaO_2, which is a more accurate measurement of oxygenation than SpO_2, as such is free. This also allows the more accurate SaO_2 value to correct some of the error that may occur due to biases sometimes seen between SpO_2 and SaO_2. In addition, the error function was modified to normalize the weight of SpO_2 measurements in the numerical minimization regardless of the number of measurements taken. SpO_2 was normalized to four measurements, as having two SpO_2 points before and after the shoulder of the $FetO_2$-SpO_2 curve is sufficient to separate shunt and $\dot{V}A/Q$ effects if the points are well spread. The modified error function is stated in equation 2.

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

Equation 2 was used for estimating parameters to calculate INVENT FiO_2 suggestions in papers II and III. The minima of equation 1 in paper I and equation 2 in papers II and III were found using a nested grid search approach with a maximum resolution of 0.01, i.e. trying all possible combinations of fA2 and fs using steps of 0.01. Figure 5 shows the same measurement data as Figure 4 but including a SaO2 measurement and the model fit using the two-parameter model and equation 2. It can be seen how the lower SD of SaO_2 means this measurement is prioritized in the fitting procedure.

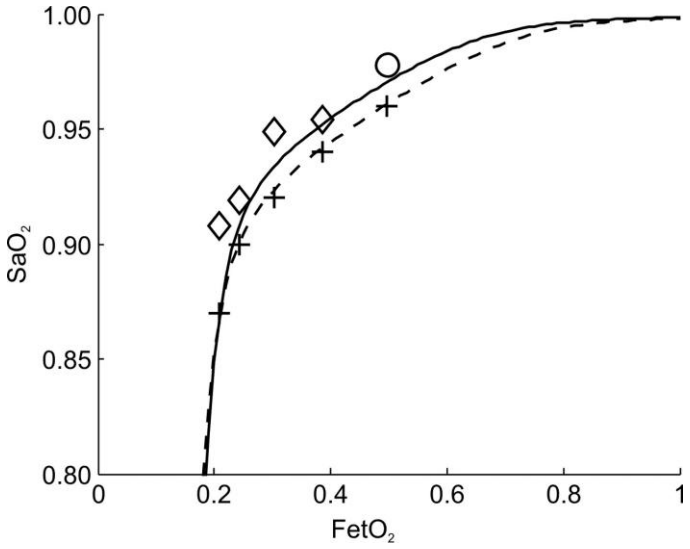

Figure 5: Example of resulting fit from estimating model parameters of the two parameter gas exchange model, to fit measured $FetO_2$-SpO_2 data (+) using equation 1 (dashed line) and equation 2 (solid line) utilizing a single SaO_2 measurement (o). The other SaO_2 measurements taken at each $FetO_2$ level are also shown (diamonds) to illustrate the improved agreement with model simulation when including a single SaO_2 in the model fitting. Patient data are the same as in Figure 4.

In paper IV, the aim was to describe pulmonary gas exchange of both O_2 and CO_2. The model was therefore fitted to both the $FetO_2$-SpO_2 curve and a single $FetCO_2$-$PaCO_2$ point. Due to the different scaling of oxygen saturations and $PaCO_2$ as well as the different effects of variation of $FetO_2$ and $FetCO_2$, the error function was limited to quantify vertical errors. The resulting error function is stated in equation 3.

$$WRSS = \frac{4}{n}\sum_{i=1}^{n}\left(\frac{(mO_{2,i} - SpO_{2,i})^2}{\sigma_{SpO_2}^2}\right) + \frac{(mO_2 - SaO_2)^2}{\sigma_{SaO_2}^2} + \frac{(mCO_2 - PaCO_2)^2}{\sigma_{PaCO_2}^2} \quad (3)$$

σ_{SpO2} was changed to 0.02 to more closely represent the variation seen in clinical studies and the accuracy reported by the manufacturer of the applied pulse oximetry device [113,114]. σ_{PaCO2} was set to 0.09 kPa [112]. Equation 3 was in paper IV minimized using a nested implementation of Brent's method [115]. Implementation of a new and faster minimization method was necessary to achieve a practical speed for parameter estimation in MatLab (Mathworks, Natick, MA). Figure 6 shows a data example from paper IV with the three parameter model fitted to oxygenation and CO_2 data by minimizing equation 3.

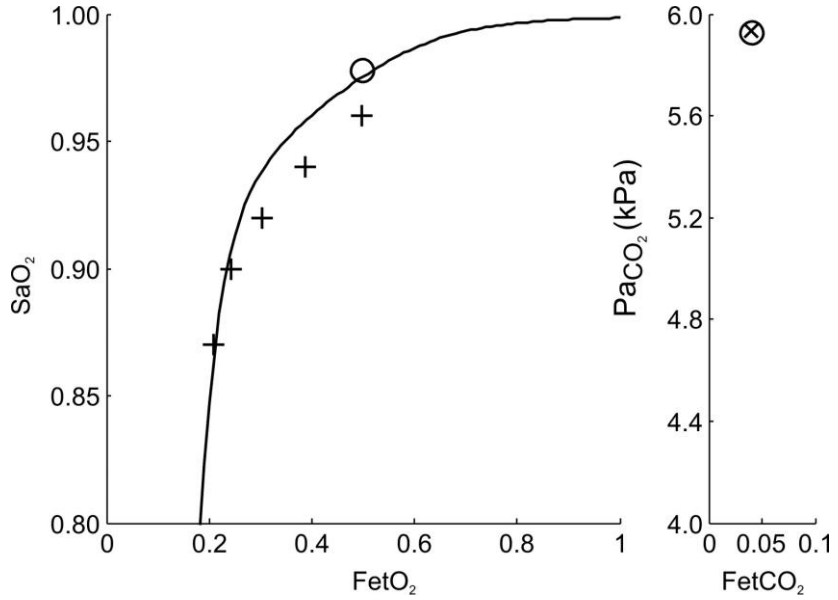

Figure 6: Example of resulting fit from estimating model parameters of the three parameter gas exchange model to O_2 and CO_2 data using equation 3. Left) Measured $FetO_2$-SpO_2 data (+) and $FetO_2$-SaO_2 point (o) and the resulting model fitted curve (solid line). Right) Measured $FetCO_2$-$PaCO_2$ point (O), and resulting model fitted simulation of $FetCO_2$-$PaCO_2$ (x).

During the experiments continuous data sampling was performed using RS-232 interfacing to retrieve: Vt and f from the ventilator (SV300 or ServoI, Marquet, Solna, Sweden, papers I-IV) or a volume meter (Elkro Gas, Salerno, Italy, paper I); SpO_2 from a pulse oximetry device (Datex AS-3, Datex-Engström, Helsinki, Finland, paper I; SC9000 critical care monitor, Siemens Medical Systems, Munich, Germany, paper III; and CO2SMO Plus, Novametrix Medical Systems, Wallingford CT, USA, papers I, II and IV); FiO_2 and $FetO_2$ from a sidestream oxygen analyzer (Datex AS-3, paper I; Oxigraf, Mountain View CA, USA, papers I-IV) and $FetCO_2$ from a sidestream gas analyzer (Oxigraf, paper IV). A minimum of one arterial blood sample was drawn during each experiment, and analyzed to obtain arterial acid-base and oxygenation

status (SaO_2, PaO_2, pHa, $PaCO_2$, CtHb, FMetHb, and FCOHb) (ABL 525, Radiometer Medical A/S, Copenhagen, Denmark, paper I; ABL 625, paper I; ABL 725, papers I, II and IV; ABL 800, paper III). The blood gas data were manually entered into the computer.

In addition, a number of model variables were assumed to be constant during the experiment. Inspired fraction of CO_2 was assumed to be 0. Atmospheric pressure was assumed to be 101.3 kPa. Saturated water vapour pressure was assumed to be 6.3 kPa [77]. Concentration of 2,3-diphosphoglycerate was set to 5 mmol/L as in normal arterial blood [110]. Anatomical dead space (VDana) and cardiac output (Q) were also assumed constant during the experiments, but were assessed differently between studies. In paper I, VDana and Q from the original studies were used [102-104]. In papers II and IV, VDana was measured by volumetric capnography (CO2SMO Plus), except for two patients in paper IV, where VDana was estimated from the average VDana/Vt ratio of the other patients. In the prospective study (paper III) volumetric capnography was not available and total apparatus and anatomical dead space was assumed to be 0.2 l, as previously used [95]. In studies II, III and IV, Q was either measured (PiCCO plus, Pulsion Medical Systems Munich, Germany) or estimated from body surface area and an assumed value of cardiac index. Body surface area was calculated from patient weight and height using the equation defined by Gehan and George [116]. CI was in papers II and III assumed to be 3.0 l/(m^2min). In paper IV CI was assumed to be 3.7 l/(m^2min), as reported in a large group of intensive care patients [117].

2.3 Decision support system

The goal of papers II and III were to evaluate INVENT for decision support of FiO_2. Therefore a new version of INVENT was implemented for this application. The structure of the system is illustrated in Figure 7. Before the system can provide suggestions on FiO_2, the two-parameter model must be identified using the parameter estimation procedure outlined above. This yields patient specific values of the fs and fA2 parameter. With parameters estimated and the patient specific variables used during parameter estimation input to the system, the physiological model may be used to simulate patient responses to changes in FiO_2. The model simulates SaO_2 and

estimates mixed venous O_2 saturation ($SmvO_2$) assuming venous pH to be 0.04 less than pHa, and mixed venous PCO_2 to be 0.8 kPa higher than $PaCO_2$.

The INVENT system uses utility theory in the form of penalty functions to model clinical preferences. Each level of FiO_2 and predicted oxygenation values are associated with a total penalty calculated as the unweighted sum of penalties due to local and general ischemia quantified as functions of SaO_2 and $SmvO_2$, respectively, and due to the risk of oxygen toxicity quantified as a function of FiO_2. The optimization component of INVENT automatically varies FiO_2 and locates the optimal level, which is that incurring minimal total penalty.

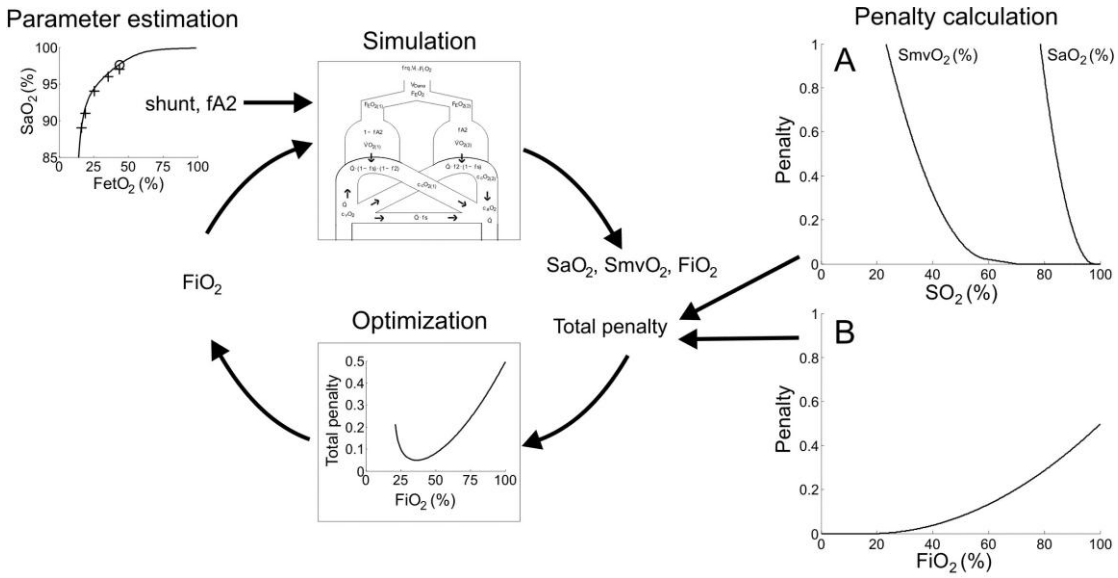

Figure 7: The structure for the INVENT system for decision support on FiO_2. Used with permission from paper II.

Figure 8 illustrates the user interface of INVENT for FiO_2 management. The figure is a screenshot taken with data input for a patient from paper III. The left hand side of the screen shows the patient specific predicted FiO_2-SaO_2 curve. On the curve a cross encircled by a green circle identifies the system suggested level of FiO_2. The system allows the clinician to manually vary the FiO_2 and see the resulting total penalty. This can be done using the button next to FiO_2 under the curve in the column "Manual". The currently selected manual FiO_2 is marked on the FiO_2-SaO_2 curve by a vertical and horizontal line. In the column "Optimal" under the curve, the system suggested level of FiO_2 is shown. Under "Manual" and "Optimal" model predicted values of SaO_2, arterial oxygen concentration (CaO_2) and oxygen delivery (DO_2) are also

shown for the manual and optimal levels of FiO_2, respectively. The manual and optimal penalties are summarized in the bar plot next to the FiO_2-SaO_2 curve. The manual FiO_2 in the screenshot corresponds to the FiO_2 selected by the attending clinician in paper III.

The right hand side shows the three penalty functions in the system, and a summary of the penalties associated with the manually selected FiO_2 level.

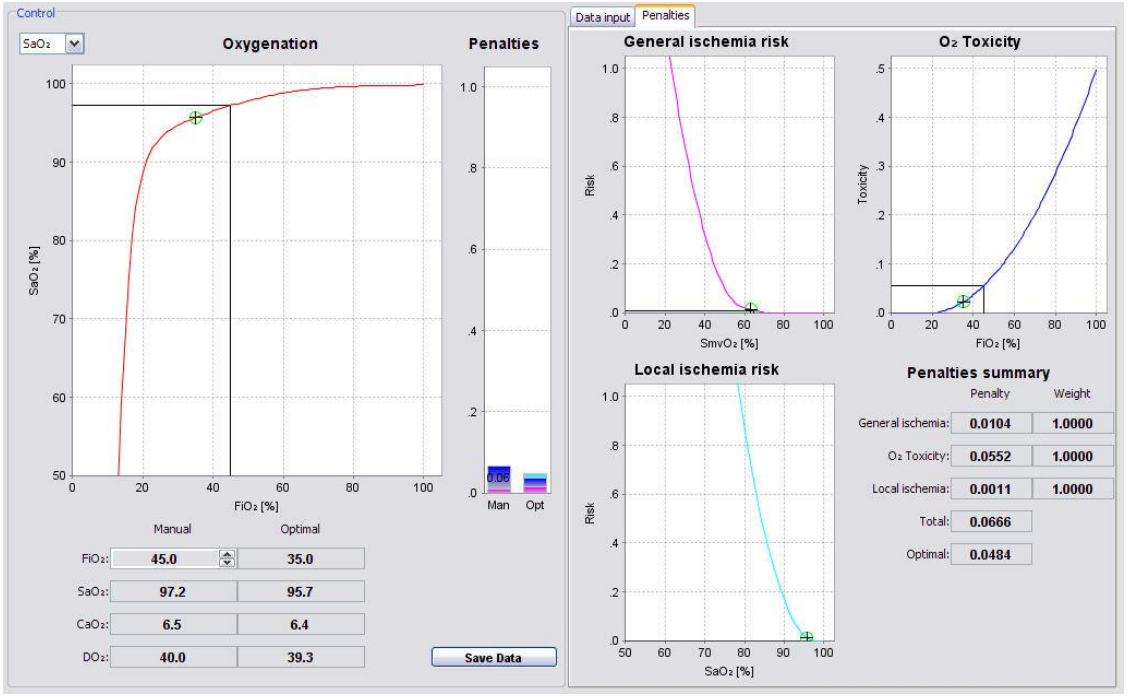

Figure 8: A screenshot of the INVENT system taken during study III. Used with permission from paper III.

2.4 ICARE system and database

The INVENT system and the parameter estimation procedure are implemented in a system, ICARE, developed at MMDS, Aalborg University [118]. The system includes software for communication with devices using RS-232 interfacing. It incorporates a MySQL database for storing all data from devices as well as model simulation data and INVENT suggestions. The system also includes autonomous agents responding to changes in specific data and calculating new values of derived variables. E.g. when a new value of height or weight is available an autonomous agent calculates a new value of body surface area. All added data are stored with an ID referring to the patient they describe. All stored data are also associated with a timestamp, a rank, and

their origin. The rank can be measured, calculated, estimated or default illustrating the quality of the data. Origin allows the user to see the device or software system, e.g. INVENT, which input the data.

3. Summary of Papers

3.1 Paper I

Aim

To evaluate the relevance of variation in the PaO_2/FiO_2 ratio with FiO_2. PaO_2/FiO_2 is the current dominating hypoxemia index used in intensive care and clinical trials. The study was also performed to evaluate the ability of a shunt only model to describe this variation in comparison with a two parameter model describing shunt and ventilation/perfusion mismatch.

Methods

The study was a retrospective evaluation. Several patient groups were included to allow the analysis to be performed simulating as many different forms of lung disorders and severities of gas exchange problems as possible. Experimental data were included from normal subjects [103], postoperative patients following gynaecological laparotomy [102,103] and cardiac surgery [103,104], patients suffering from cardiac incompensation [103], intensive care patients from a previously published study [103] and previously unpublished experimental data from a further 8 intensive care patients (see paper II, section 3.2) totaling 93 patients studied. A total of 36 patients were mechanically ventilated intensive care patients whereas 57 were spontaneously breathing. Some of the patients were studied on more than one occasion, e.g. after changes in PEEP, yielding a total of 134 patient cases. 18 patient cases (spontaneous breathing) were excluded as measurement data only included arterial blood gas measurements at two levels of FiO_2.

First the two-parameter model was used to show the theoretical variation in PaO_2/FiO_2 upon changing FiO_2 under different levels of shunt and $\dot{V}A/Q$ mismatch. The variation was analysed in a clinically relevant range, which was defined as the range of FiO_2 corresponding to simulated SaO_2 values in the range 92-98%. The variation was then analysed in 116 patient cases, using both the one parameter 'effective' shunt model and the twoparameter model to fit patient data and simulate variation in PaO_2/FiO_2 ratio. The value of the PaO_2/FiO_2 ratio as hypoxemia index was then evaluated by classifying each patient as being normal (PaO_2/FiO_2 > 47 kPa),

having mild hypoxemia (40 kPa ≤ PaO_2/FiO_2 < 47 kPa), ALI (27 kPa ≤ PaO_2/FiO_2 < 40 kPa) or ARDS (PaO_2/FiO_2 < 27 kPa) [1]. This was done at the minimum and maximum FiO_2 of the patient specific clinically relevant ranges, and the number of patients changing classification from low to high FiO_2 were quantified.

Data are reported as means ± SD appearing normally distributed on graphic evaluation of Q-Q plots [119]. F-tests were used to compare goodness of fit between the shunt-only model and the two parameter model, taking into account the degrees of freedom lost with additional complexity. A confusion matrix [120] was used to illustrate the number of patients classified as normal, with mild hypoxemia, ALI or ARDS upon changing FiO_2. A cut-off value of 0.05 was used for signifying statistical significant differences in the F-test.

Results

Figure 9 and Figure 10 illustrate the theoretical variation in SaO_2 and PaO_2/FiO_2 ratio upon changing FiO_2 under different levels of shunt and $\dot{V}A/Q$ mismatch, respectively. Figure 11 illustrates measured and model simulated variation in SaO_2 and PaO_2/FiO_2 in six patients representing typical examples from the studied patient groups. The two parameter model was shown to give a statistically better fit to data than the 'effective' shunt model (P < 0.005).

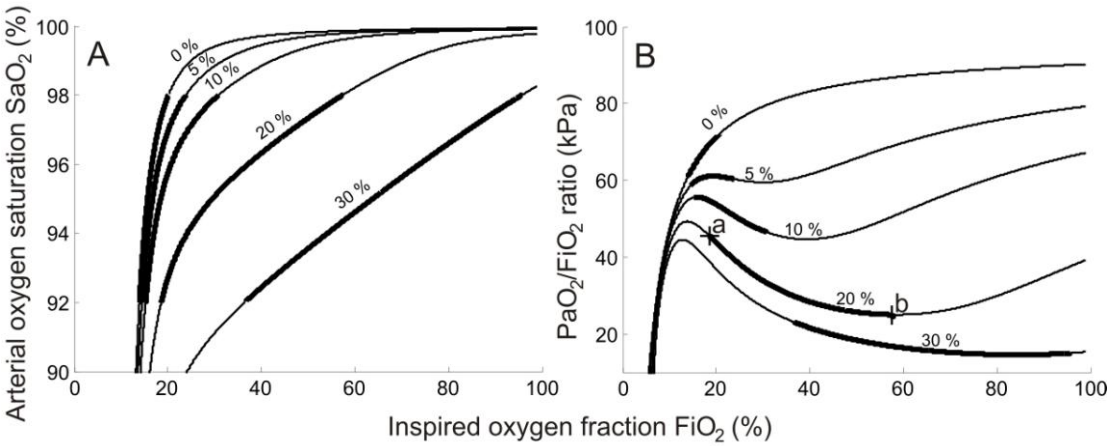

Figure 9: Simulated variation in SaO_2 (A) and PaO_2/FiO_2 ratio (B) upon changing FiO_2 under varying levels of shunt (fs). Thick solid lines indicate the portion of the curves within the clinically relevant range of FiO_2. a and b in subplot B indicate a variation in FiO_2 from 0.19 to 0.57 for fs=20%. Simulations were performed using ΔPO_2 = 0 kPa (fA2=0.9), VO_2 = 0.26 l/min, alveolar minute volume = 5.25 l. Used with permission from paper I.

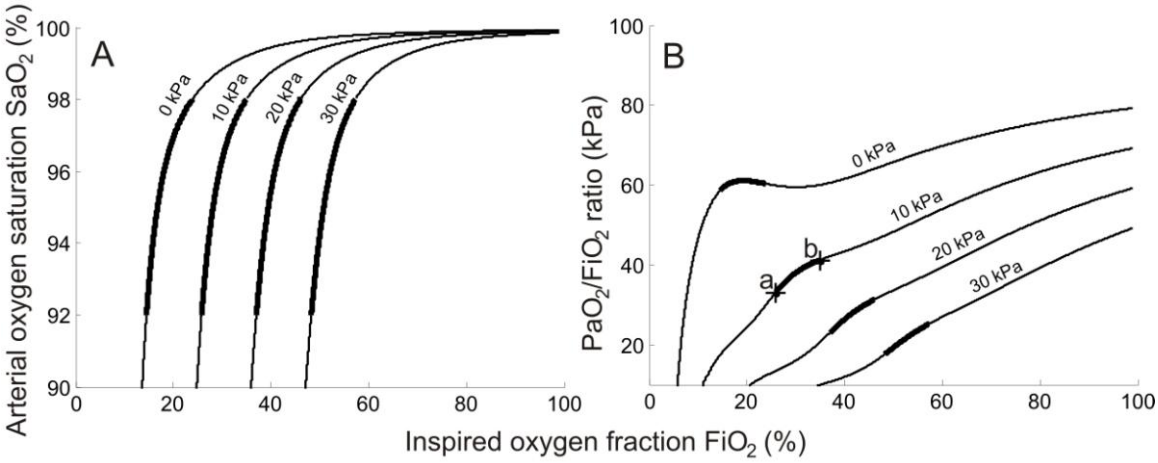

Figure 10: Simulated variation in SaO_2 (A) and PaO_2/FiO_2 ratio (B) upon changing FiO_2 under varying levels of $\dot{V}A/Q$ mismatch (ΔPO_2). Thick solid lines indicate the portion of the curves within the clinically relevant range of FiO_2. a and b in subplot B indicate a variation in FiO_2 from 0.26 to 0.35 for fs=20%. Simulations were performed using fs = 5 %, VO_2 = 0.26 l/min, alveolar minute volume = 5.25 l. Used with permission from paper I.

Disease classification changed upon varying FiO_2 within the clinically relevant range in 38 of the 116 patient cases (~30%) according to the two-parameter model. The number of patient cases classified as ALI or ARDS according to the two-parameter model changed from 23 to 31 (~35% increase) and from 18 to 24 (~33% increase), respectively.

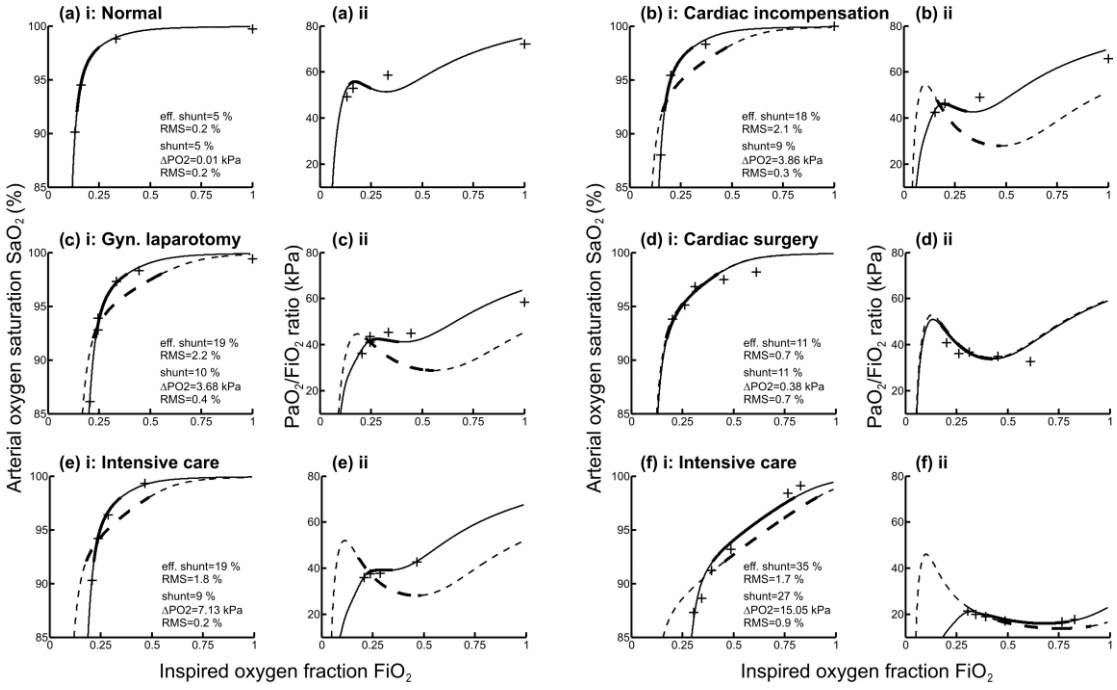

Figure 11: Model simulations and measured patient data, for six patients representing typical cases. i: Measured and simulated variation in SaO_2 with changes in FiO_2. ii: Measured and simulated variation in PaO_2/FiO_2 with changes in FiO_2. (a): Normal subject [103], (b): cardiac incompensation subject [103], (c): Gynaecological laparotomy patient [102,103], (d): cardiac

surgery patient [104], (e): intensive care patient [103], (f): patient from the previously unpublished study in intensive care patients. Solid lines and dashed lines indicate models simulations with the two-parameter model, and the 'effective' shunt model, respectively, thick part of curves correspond to the clinically relevant range of FiO_2. Model parameters and root mean square (RMS) error are specified for each model. + represent measured patient data. Used with permission from paper I.

Conclusions

The PaO_2/FiO_2 ratio is dependent on both the levels of FiO_2 and SaO_2. Within the ranges investigated (SaO_2 = 92-98 %) almost a third of patients change disease classification. Therefore the scientific and clinical utility of the PaO_2/FiO_2 ratio appears questionable. If used, then at least the FiO_2 level at which the ratio was measured should be reported. The results indicate that the one-parameter 'effective' shunt model is not capable of describing this variation correctly, but that the two parameter model is.

3.2 Paper II

Aim

To retrospectively evaluate INVENT for the ability to provide appropriate suggestions of FiO_2 in intensive care patients.

Methods

Patient data were used from a study in intensive care patients. Data from 8 of the patients had been used in paper I, the remaining were previously unpublished. The study had been approved by the ethical committee of North Jutland and Viborg Counties and the ethical committee of Copenhagen. Informed consent was obtained from relatives or nearest guardian. The study inclusion criteria were eighteen years of age or more and requirement of mechanical ventilation with levels of FiO_2 higher than 0.4. Exclusion criterion was a highly dynamic patient condition potentially affecting measured respiratory parameters during the experiment. This was secured by excluding patients with base excess less than -6 mmol/L and serum lactate level greater than 4 mmol/L. Measurement data were used from 18 intensive care patients with ALI. Two of the 18 patients were excluded as malfunction of the data collection software had prevented successful experiments. The patients had been studied at Rigshospitalet (Copenhagen, Denmark), as part of a protocol investigating the effects of changes in PEEP. Therefore in several of the patients measurement data were available at two PEEP settings, and a total of 27 patient cases were available, and used in the retrospective evaluation. Median age and weight of the patients were 64.5 years (range 27-85 years) and 80 kg (range 70-140 kg), respectively.

The two parameter model was fitted to patient data (SpO_2 and a single SaO_2), and INVENT was used to calculate the suggestion of FiO_2 (FiO_2^{sugg}). This was compared to the FiO_2 level and corresponding SaO_2 values used in clinical practice (FiO_2^{clin}, SaO_2^{clin}). An additional model fit was also performed in each patient case fitting the model to measured SaO_2 values at each FiO_2 level, representing the best possible model description of the patient. This model fit was used to calculate the 'true' resulting SaO_2 (SaO_2^{true}) from using INVENT advice. As such, this allowed an estimate of the effect of using SpO_2 combined with a single SaO_2 value in model fitting to predict patient response to changes in FiO_2.

Data are reported as median (range) as they did not appear normally distributed on graphic evaluation of Q-Q plots. Wilcoxon matched pairs tests were used to compare INVENT FiO_2 and SaO_2 values with clinician FiO_2 and SaO_2. Bland-Altman plots [121] were used to evaluate the agreement between SpO_2 and SaO_2. A cut-off value of 0.05 was used for signifying statistical significant difference.

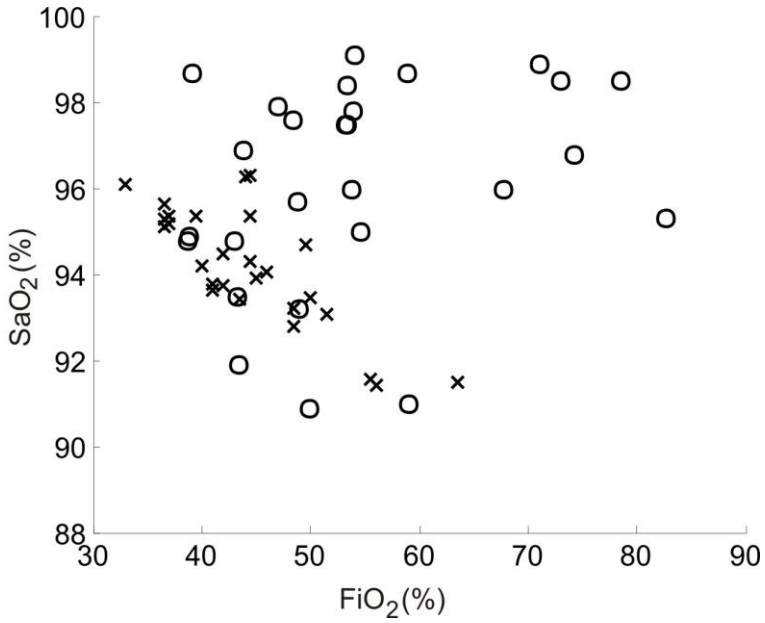

Figure 12: Scatter plot of measured FiO_2^{clin} versus measured SaO_2^{clin} (o), and $FiO_2^{\prime sugg}$ versus model simulated resulting SaO_2^{sugg} (x). Used with permission from paper II.

Results

Figure 12 shows a scatter plot of FiO_2 levels selected in clinical practice plotted against corresponding measured SaO_2 values and INVENT suggested FiO_2 levels plotted against model simulated SaO_2 values. The same is shown in Figure 13 but with model simulated SaO_2 replaced by the simulated 'true' resulting SaO_2 values. Table 1 reports the median and ranges of measured and simulated FiO_2 levels and SaO_2 values.

FiO_2^{clin} and FiO_2^{sugg} as well as SaO_2^{clin} and SaO_2^{sugg} were significantly different ($P<0.01$). SaO_2^{sugg} and SaO_2^{true} were also significantly different ($P<0.05$). The scatter plots and ranges of the values show that ranges of INVENT FiO_2 and SaO_2 values are narrower than those used in clinical practice. INVENT maintained FiO_2 below 60 % in all cases but one where the system used 64 %, whereas FiO_2 levels higher than 70

% were used in several patients in clinical practice. All measured and simulated SaO_2 values were above 89 %.

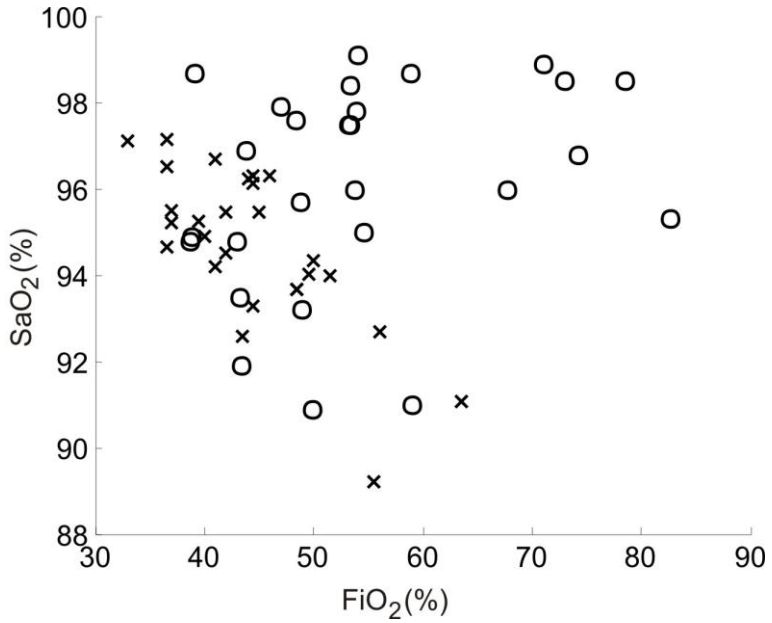

Figure 13: Scatter plot of FiO_2^{clin} versus SaO_2^{clin} (o), and FiO_2^{sugg} versus model simulated 'true' resulting SaO_2^{true} (x). Used with permission from paper II.

Table 1. Median and range of clinical and INVENT values. Adapted from paper II with permission.

	Median	Min	Max
FiO_2^{clin} (%)	53.3	38.6	82.6
FiO_2^{sugg} (%)	44	33.0	63.5
SaO_2^{clin} (%)	96.8	90.9	99.1
SaO_2^{sugg} (%)	94.2	91.4	96.3
SaO_2^{true} (%)	94.9	89.2	97.1

Conclusions

INVENT suggests appropriate levels of FiO_2 and SaO_2, acting to minimize risk of oxygen toxicity whilst maintaining adequate oxygenation. Although using pulse oximetry to estimate arterial oxygen saturation introduces noise in model predictions, the resulting SaO_2 values remain within safe ranges in all patients.

3.3 Paper III

Aim

To prospectively evaluate the ability of INVENT to provide appropriate suggestions of FiO_2 in intensive care patients.

Methods

The study was performed from November 2007 to March 2009 in a four-bed intensive care unit at Aalborg Hospital (Aalborg, Denmark). Inclusion criteria were broad and there were few exclusion criteria in order to evaluate INVENT in a patient population covering patients normally residing in an ICU. Inclusion criteria were eighteen years of age or more and requirement of mechanical ventilation. Patients were excluded if they required an FiO_2 level higher than 0.8. The other exclusion criteria were clinical suspicion of lung emboli, critical hemodynamic status, and pregnancy, all being cases where the physiological model has not been validated yet. A total of 15 patients were included, two of which were excluded before data analysis. In addition, a single experiment was excluded, as the patient was turned during the experiment affecting the gas exchange status of the patient. Up to four experiments were performed in each patient totaling 45 patient cases available for analysis.

Patients were studied over two consecutive days performing two experiments per day. In each experiment both INVENT and the attending clinician managed FiO_2 shifting sequence between experiments. Between INVENT and clinician FiO_2 management, FiO_2 was reset to baseline level and 5 minutes was allowed for equilibration [77]. An arterial blood gas measurement was taken at baseline and 5 minutes after each change in FiO_2.

Data are reported as means ± SD or as median (interquartile range [range]) if not appearing normally distributed on graphic evaluation of Q-Q plots. A box and whisker plot was used to compare overall FiO2 changes from baseline level by attending clinicians and INVENT [119]. Linear regression was used to analyse the relationship between selected FiO_2 levels and resulting measured SaO_2 values for baseline, attending clinicians and INVENT. Pearson correlation coefficients were calculated to quantify the strength of these linear relationships.

Results

Median time between two consecutive experiments was 74 (60-123 [50-302]) minutes. Attending clinicians varied FiO_2 in 22 out of the 45 experiments (49 %), whereas INVENT varied FiO_2 in 43 experiments (96 %) showing a more frequent response to changes in patient state by INVENT. Both attending clinician and the INVENT selected to change FiO_2 in 20 out of the 45 experiments (44 %). These changes were all in the same direction from baseline level. There were no experiments where attending clinicians and INVENT selected opposite directions of changes in FiO_2.

INVENT was more prone to change FiO_2 from baseline level and to make larger changes compared to attending clinicians, as illustrated in the box and whisker plot in Figure 14.

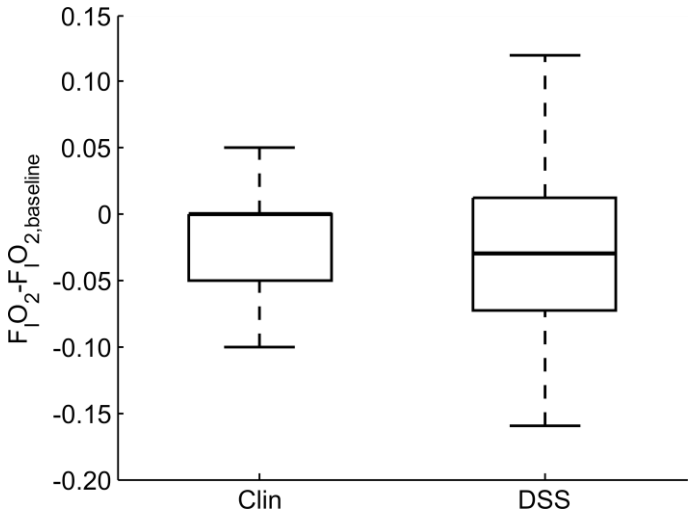

Figure 14: Box and whisker plot of changes in FiO_2 from baseline level by attending clinicians (Clin) and INVENT (DSS). Used with permission from paper III.

Figure 15 illustrates scatter plots of baseline, clinician and INVENT selected levels of FiO_2 versus measured values of SaO_2, allowing an evaluation of the reasonableness eness of INVENT advice compared to clinicians on a population basis. Both the ranges of selected FiO_2 and resulting SaO_2 were narrower for INVENT in comparison with baseline and clinician ranges. Linear regression lines are also shown, illustrating the compromise of balancing FiO_2 and SaO_2. The resulting linear models and Pearson correlation coefficients with P-values were: for baseline: $SaO_2 = -0.036\ FiO_2 + 0.976$ (-0.159, P = 0.296); for attending clinicians: $SaO_2 = -0.026\ FiO_2 + 0.968$ (-0.142, P =

0.351); and for INVENT: SaO_2 = -0.111 FiO_2 + 1.001 (-0.579, P < 0.001), showing that only the correlation for INVENT was statistically significant.

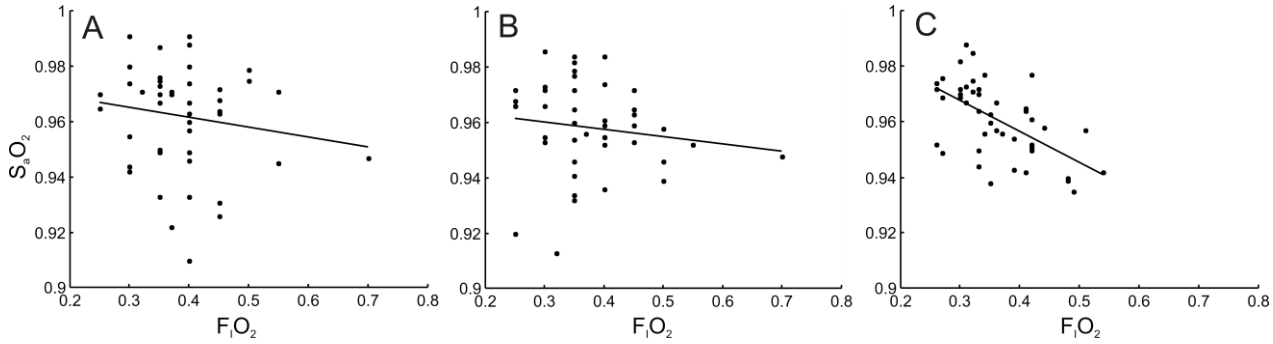

Figure 15: Scatter plots of FiO_2 versus measured SaO_2 in each patient case: A) at baseline, B) set by attending clinicians, and C) set following INVENT suggestions. Solid lines illustrate linear regressions for the relationship between FiO_2 and SaO_2. Used with permission from paper III.

Interesting differences emerged when looking at selected levels of FiO_2 and measured SaO_2 on an individual patient basis during the four experiments. Figure 16 illustrates clinician (Figure 16A, B) and INVENT (Figure 16C, D) FiO_2 and SaO_2 in 6 of the patients. For example, in one patient, INVENT was more capable of preventing a large drop in SaO_2 due to change in patient status between experiments (patient illustrated by squares), in another case, INVENT seemed too prone to increase FiO_2 from a low level when it was not necessary (patient illustrated by dots).

As an interesting technical note aside, Figure 17 illustrates a Bland-Altman plot of the agreement between model predicted values of SaO_2 and the resulting measured values. The model predicted on average somewhat lower SaO_2 with a mean difference of -0.005 ± 0.012. No systematic bias can be identified from the plot. This plot was not included in paper III.

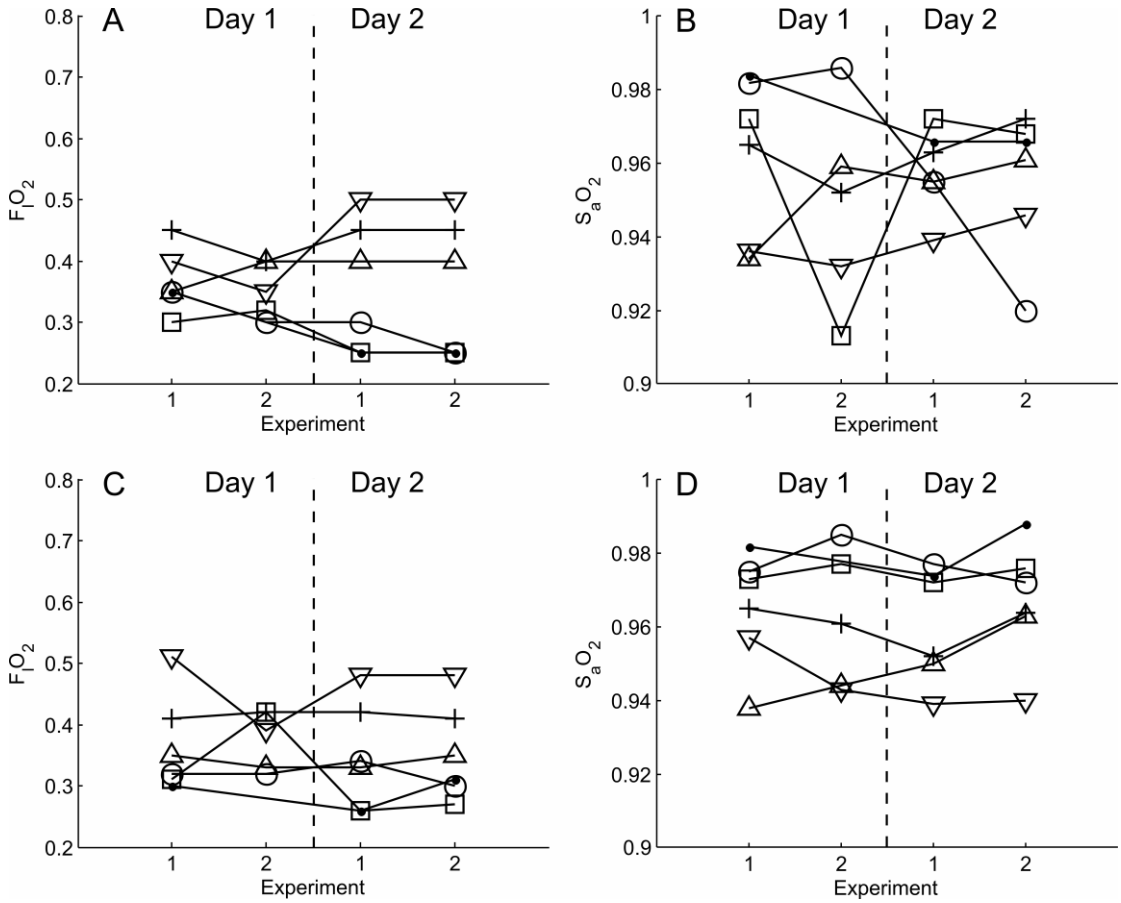

Figure 16: Selected levels of FiO_2 and SaO_2 in the four experiments in 6 of the patients. A) and B) clinician FiO_2 and SaO_2, respectively. C) and D) INVENT FiO_2 and SaO_2, respectively. Used with permission from paper III.

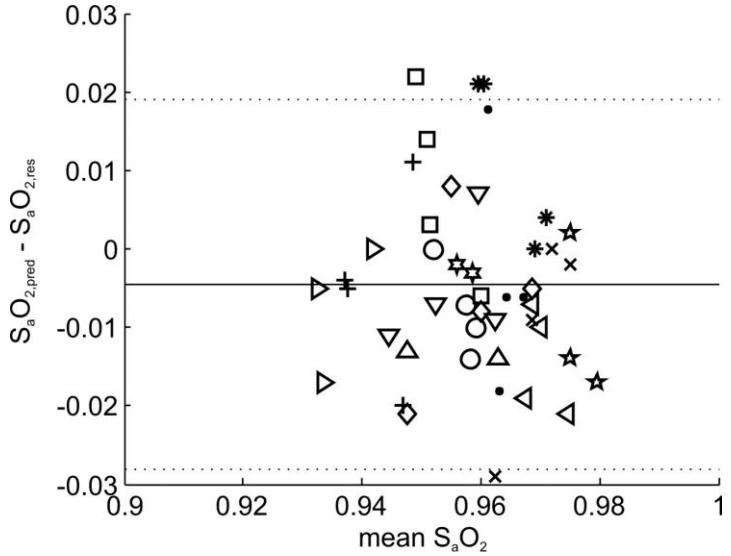

Figure 17: Bland-Altman plot of agreement between model predictions of SaO_2 ($SaO_{2,pred}$) and measured resulting SaO_2 ($SaO_{2,res}$) from using INVENT FiO_2 suggestions. Values on the x-axis are the average SaO_2 of each set. Solid line is the average difference across all patient cases and dotted lines are the limits of agreement (average difference ± 2SD). Patient cases from the same patient are shown with identical point markers. Used with permission from paper III.

Conclusions

Results indicate that the INVENT system is safe to use for suggesting FiO_2 levels in intensive care patients. The physiological model accurately predicts SaO_2, and all FiO_2 levels suggested by INVENT resulted in appropriate values of SaO_2. Both clinicians and INVENT often changed FiO_2 when evaluating patients suggesting that frequent reevaluation of the patients is valuable. INVENT may help to understand difficult patients, and in easily managed patients the system may be used to free the focus of clinicians to concentrate on more challenging therapy.

3.4 Paper IV

Aim

To perform a systematic comparison of different minimal models to find the necessary degree of modeling complexity to describe the pulmonary gas exchange of both O_2 and CO_2 and provide an adequate description of gas exchange abnormality in intensive care patients.

Methods

The study was carried out as a retrospective study. The data used in paper II were selected, as these patients had severe disorders in pulmonary gas exchange. After publication of paper II the data from two additional patients were made available totaling 18 patients for the analysis. As several patients had been studied at two levels of PEEP a total of 30 patient cases were available.

Three different models were compared: an one parameter 'effective' shunt model (Model I); a two parameter model as used in papers I, II, and III describing shunt and $\dot{V}A/Q$ mismatch, with perfusion locked between two ventilated compartments, and fraction of ventilation varied to fit patient data (model II); and a three parameter model, similar to model II but where also the fraction of perfusion going to the two ventilated compartments is varied to fit patient data. The three models were compared quantitatively for their ability to fit patient data taking into account the degrees of freedom lost with increasing complexity, and qualitatively for their ability to describe the gas exchange abnormality of the individual patients.

Data are reported as means ± SD appearing normally distributed on graphic evaluation of Q-Q plots. F-tests were used to compare goodness of fit between models, taking into account the degrees of freedom lost with more complex models. χ^2 tests were also used to evaluate the goodness of fit of the models on a patient case basis. A Bland-Altman plot was used to evaluate the agreement between SpO_2 and SaO_2. A cut-off value of 0.05 was used for signifying statistical significant differences in F-tests. In the χ^2 tests $P>0.1$ was used as cut-off for signifying an adequate fit to measurement data.

Results

Chi-squared tests of quality of fit to individual patient cases indicated adequate fit to measured data (P>0.1) in 1 patient case for model I (3% of cases), 19 (63%) patient cses for model II and in 24 (80%) patient cases for model III. Pairwise F-test comparisons showed model II to give a significantly better fit to measured data than model I (P<0.001), and indicate model III to give better fit than model II (P<0.1), however with low statistical significance.

Figure 18 shows an example of model fits to measured O_2 and CO_2 data in a patient case where only model III provides an adequate fit to both O_2 and CO_2. Both models II and III fit the CO_2 data, but model II can not simulate sufficient right shift in the $FetO_2$-SpO_2 curve, i.e. describe a sufficient alveolar to lung capillary drop in PO_2.

Of the 6 patient cases where chi-squared tests showed that model III produced an inadequate fit to data, 1 patient could be described by model I, i.e. shunt was sufficient to describe the data. In another case, model II was sufficiently complex to describe measured data. In the last 4 patient cases, there was a significant bias between SpO_2 and SaO_2. However, in these cases fitting model III to SaO_2 showed small differences in resulting described degree of lung disorder according to the difference between alveolar and arterial partial pressures of O_2 and CO_2.

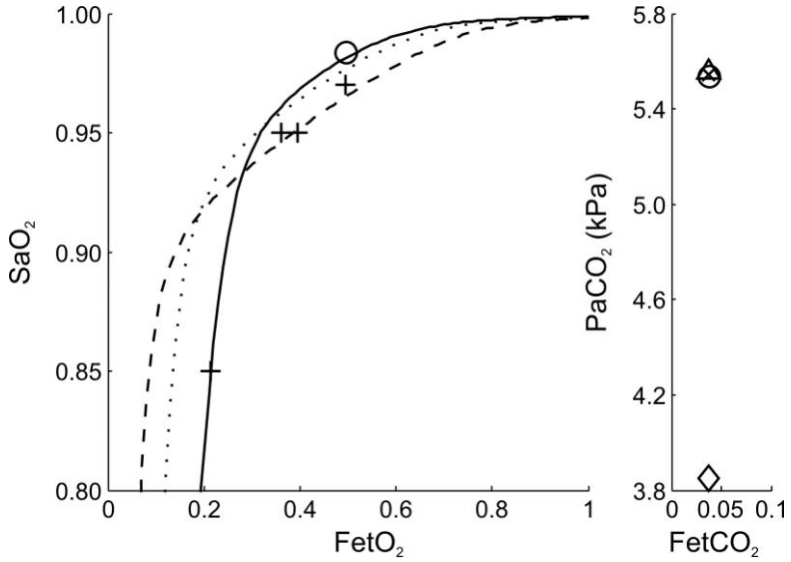

Figure 18: Fit of the three models to measured patient data, in a patient case, where only model III provides a good fit to both O_2 and CO_2 data. Left) Model fitted simulations of oxygenation for model I (dashed line), model II (dotted line) and model III (solid line), and measured $FetO_2$-SpO_2 (+) and $FetO_2$-SaO_2 (o) points. Right) Model fitted simulations of $FetCO_2$-$PaCO_2$ for model I (diamond), model II (triangle) and model III (x) and measured $FetCO_2$-$PaCO_2$ (o) point.

Figure 19 shows model fitted ventilations and perfusions of the two ventilated compartments versus $\dot{V}A/Q$ of the respective compartments for models II and III. For each patient case there are two points in each sub plot: one for the low $\dot{V}A/Q$ compartment and one for the high $\dot{V}A/Q$ compartment. The ranges of $\dot{V}A/Q$ ratios that model III can describe are broader than those of model II. This is in particular obvious in the middle ranges of $\dot{V}A/Q$ ratios when comparing ranges of perfusion (A and C), and in the lowest range of $\dot{V}A/Q$ ratios when comparing ventilation (B and D).

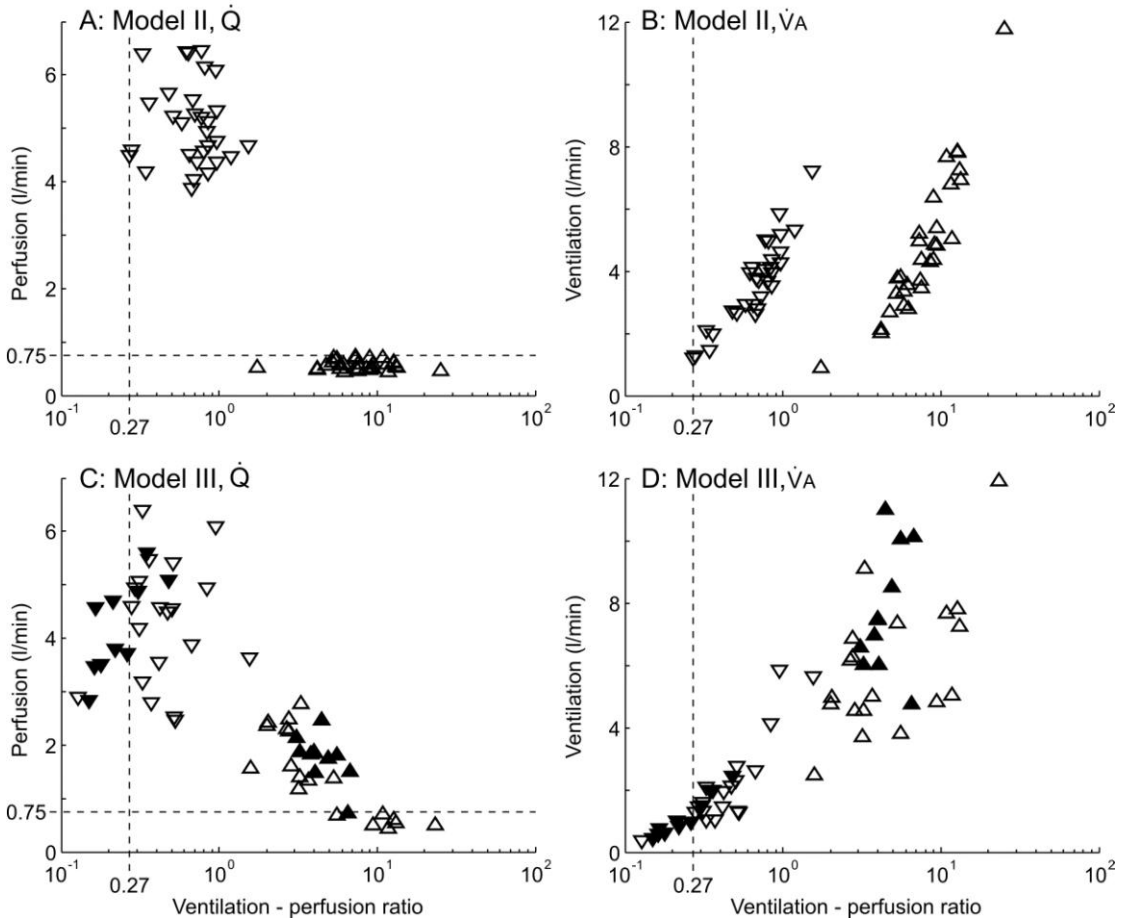

Figure 19: Model fitted perfusion and ventilation of ventilated compartments 1 (upward triangles) and 2 (downward triangles) versus ventilation/perfusion ratios in the respective compartments. A: perfusion to ventilated compartments of model II. B: ventilation to ventilated compartments of model II. C: perfusion to ventilated compartments of model III. D: ventilation to ventilated compartments of model III. Filled triangles indicate patient cases where Chi-squared tests of quality of fit resulted in p>0.1 for model III and p<0.1 for model II, or where the resulting p for model III was at least 0.2 larger than that for model II.

Conclusions

The results show that the one parameter model is not able to describe pulmonary gas exchange of O_2 and CO_2. The two parameter model is sufficiently complex to describe gas exchange of one of the two gases, but is not able describe gas exchange of both gases in all patients. The three parameter model is able to provide adequate fits to measured O_2 and CO_2 data, and is robust in the cases where SpO_2 provide a poor estimate of SaO_2. The three parameter model is able to provide a more varied description of $\dot{V}A/Q$ ratios in different patients. As such this minimal model represents a good compromise between complexity and feasibility, and may be used in clinical practice to describe lung status in patients with severe lung disorders.

4. Discussion

Ventilator management can be considered a process of finding the appropriate compromise between conflicting goals, it is important to secure gas exchange, but at the same time excessive levels of pressures, volumes and FiO_2 should be avoided to prevent VILI. This is a complex task requiring a good understanding of the pathophysiology of the individual patient. Although numerous measurements are available in the ICU to describe the gas exchange status of the lungs, currently available measurements are over-simplified and vary with changes in therapy not affecting lung status. Model-based DSSs constitute a potential solution by offering a deeper understanding of the patient's lung status and by integrating measurement data and suggesting optimal therapy.

The overall aim of this PhD project was to evaluate the use of minimal models of gas exchange in decision support of ventilator management. Four questions were addressed during the project, see section 1.5. In the following the answers to these four questions are discussed based on the results presented in the four papers. In the following sections the INVENT system as well as results of the PhD project are discussed in relation to: rule-based DSSs and other model-based DSSs. In addition, this chapter will discuss the necessary future work to allow INVENT to provide decision support of FiO_2, Vt and f in intensive care patients, and what is necessary to also provide suggestions on PEEP. As a final discussion on decision support, this chapter will discuss the necessary steps to be taken to achieve a successful integration of INVENT in clinical practice. This chapter will also examine the limitations of the mathematical models and parameter estimation methods used in all the studies presented in this thesis. Finally other relevant clinical perspectives related to the project are discussed.

4.1 The major findings of this thesis

Paper I shows that the currently dominating oxygenation index, the PaO_2/FiO_2 ratio varies significantly with changes in FiO_2. This has been shown both theoretically, according to a two parameter gas exchange model describing shunt and $\dot{V}A/Q$ mismatch, but also in various patient groups including intensive care patients. The clinical and scientific value of the index therefore appears doubtful. A shunt only

model can not describe this variation accurately, but the two parameter model can. The results presented in paper I illustrate that a two parameter gas exchange model is necessary to accurately predict changes in oxygenation with FiO_2, and is therefore the necessary complexity for decision support of FiO_2 in the ICU.

A two parameter model describing shunt and $\dot{V}A/Q$ mismatch is an integrated part of the INVENT system originally presented by Rees et al. [73]. As a first step towards clinical integration INVENT was modified in this PhD to provide decision support of FiO_2. This version of INVENT is based on the two parameter gas exchange model alone to predict patient response to changes in FiO_2. In addition, the parameter estimation procedure was modified to include arterial oxygen saturation measured from an arterial blood sample. Paper II describes the retrospective evaluation of INVENT for decision support of FiO_2 in intensive care patients. The results indicate that INVENT suggests appropriate levels of FiO_2 and SaO_2. However, the study was retrospective and resulting oxygenations were predicted by model simulations, therefore the study is limited to indicate that INVENT is safe to use in an ICU.

Paper III presents the prospective evaluation of INVENT for providing decision support of FiO_2 in 13 intensive care patients in up to four experiments over two consecutive days. Although the number of patients was limited, the results indicate that INVENT provides safe and appropriate suggestions of FiO_2 in intensive care patients with varying severities of respiratory failure. The scatter plots illustrating INVENT FiO_2 versus resulting SaO_2 (Figure 15C) show that INVENT standardizes the compromise of achieving sufficient oxygenation versus avoiding the adverse effects of hyperoxia, these compromises being patient specific as INVENT suggestions are based on model parameters estimated to describe the individual patient. When higher FiO_2 is required, INVENT accepts lower SaO_2. Both in the retrospective and the prospective study, it appears that INVENT managed this balance as well as or better than attending clinicians.

INVENT was originally designed to provide decision support of FiO_2, Vt and f [73]. To provide appropriate suggestions of Vt and f, it is necessary to also model the pulmonary gas exchange of CO_2 as changes in alveolar ventilation caused by changes

in Vt and f modify gas exchange of CO_2 and thereby affect the acid-base status of the blood. Paper IV describes a systematic evaluation of what modeling complexity is necessary to obtain an accurate minimal model representation of pulmonary gas exchange of both O_2 and CO_2. The results presented in paper IV show that a three parameter model describing shunt and $\dot{V}A/Q$ mismatch can accurately describe O_2 and CO_2 gas exchange in intensive care patients. The two parameter model describing shunt and $\dot{V}A/Q$ mismatch was sufficient in the majority of patient cases but failed in some. In comparison, the three parameter model can describe broader ranges in $\dot{V}A/Q$ ratios and is able to describe perfusion to a model compartment with very low $\dot{V}A/Q$ ratios, close to 0.1. This is an interesting quality as perfusion of lung regions with very low $\dot{V}A/Q$ ratios has been described in ARDS patients in studies using the MIGET technique [94,95]. The two parameter model could not provide such a physiological description.

4.2 Model-based or rule-based decision support systems?

The successful prospective evaluation of INVENT for suggestions of FiO_2 is an important indication of the clinical usability of a model-based DSS. However, in comparison numerous clinical trials have been performed with rule-based systems including large multicenter studies and often in complex problems involving several ventilator settings. Rule-based systems have also been successfully implemented in commercial ventilators. Development of a model-based decision support system is a complex and time-consuming task involving mathematical description of a complex physiological system, quantification of clinical preferences and development of methods for estimating model parameters from clinical data. Indeed, given the current status of rule-based systems compared to model-based systems one may ask, is it still worth it?

There is no doubt that under certain conditions use of a rule-based system may result in improvement in patient care [e.g. 47,53] and in general standardize care, which is a quality in itself [40]. Multicenter studies have also shown that this can be achieved with the same system successfully across several institutions [47,53]. It may also be argued that compared to a model-based DSS, a rule-based DSS in the simplest form is of relatively low cost to build, for example by implementing a computerized version

of a clinical guideline. However, rule-based systems remain blackbox systems, which do not provide the clinician with a deeper understanding of the patient nor the provided advice. Implementation of intelligent graphic user interfaces have been suggested to address this problem [67], however, graphic interfaces do not help clinicians in understanding the provided advice, and would likely be more valuable with an underlying physiological interpretation of the patient as in a model-based DSS.

When estimated, the model parameters for the two parameter gas exchange model used in INVENT provide a physiological interpretation of the individual patient. The fs parameter quantifies the degree of intrapulmonary shunt, and the fA2 parameter describes the degree of $\dot{V}A/Q$ mismatching. This is directly related to the response of the individual patient to changes in FiO_2, as increases in intrapulmonary shunt causes a vertical depression of the FiO_2-SaO_2 curve, i.e. changes in FiO_2 have less effect on SaO_2. An increase in $\dot{V}A/Q$ mismatching (low fA2) causes a horizontal right shift in the FiO_2-SaO_2 curve. This can be translated to a ΔPO_2 value, which describes the extra amount of oxygen necessary at the mouth to counter the oxygenation problem due to $\dot{V}A/Q$ mismatch.

The requirement of a parameter estimation procedure may be regarded as a limitation of model-based DSS compared to rule-based DSSs. The parameter estimation procedure used to identify the two parameter gas exchange model in INVENT requires variation in FiO_2 and measurement of oxygenation using pulse oximetry, a single arterial blood gas analysis and measurement of oxygen fraction in the expired air. Variation of FiO_2 is a common procedure in an ICU and only measurement of expired gas fractions can be considered not a part of routine clinical data. However, these measurements can be obtained from medical equipment, and as shown in paper I, they are necessary for an accurate description of pulmonary gas exchange. In addition, the parameter estimation procedure could safely be performed by a nurse, and Bayesian methods have been developed for supporting the selection of FiO_2 steps and potentially making the procedure computer controlled [122]. Of course, clinicians or nurses could vary FiO_2 without a computer system to better understand patient responses to changes in FiO_2. This would, however, be time-demanding requiring

resources not normally available in clinical practice. Without tools as those presented by Rees et al. [78] to monitor equilibration after changes in FiO_2, it is necessary to allow 5 minutes for equilibration [77] prolonging the process compared to using the DSS. In addition, although varying FiO_2 without a DSS would give clinicians a better understanding of the gas exchange status of the patient, it would not help to standardize clinical preferences when managing FiO_2.

Another possible advantage of model-based DSS is removal of the need for a trial and error approach to locating the appropriate ventilator settings [68]. However, this is under the assumption that the physiological models accurately predict patient response to changes in therapy. The good agreement between model simulated SaO_2 from fit to pulse oximetry with model simulated SaO_2 from fit to SaO_2 reported in paper II (Figure 12 and Figure 13) indicate that the two parameter gas exchange model accurately predicts patient response to changes in FiO_2. This was confirmed in the prospective study as shown in Figure 17.

INVENT uses utility theory in the form of penalty functions to decide therapy. The penalty functions in INVENT quantify clinical preferences, e.g. preventing ischemia. The suggestions provided by INVENT are associated with penalties calculated using the relevant penalty functions. As such, the compromises between conflicting goals made by INVENT are made explicit to the clinician allowing an understanding of the provided advice.

4.3 Current status of model-based decision support of mechanical ventilation

Several model based DSS or hybrid systems combining models with rules have been developed to assist clinicians in managing mechanical ventilation as outlined in the introduction. In the following, the various qualities of the systems are discussed including how the results obtained in the PhD project contributes to the field of model-based decision support of mechanical ventilation. The different systems are not directly comparable for their ability to provide appropriate suggestions of changes in therapy as they provide advice for different ventilator settings, use different measurements for evaluation or have been tested under different conditions. In the

following discussion the systems are instead compared with regards to the potential clinical benefits they may provide and their clinical feasibility. The VentPlan system [71] was very similar to INVENT in terms of modeling and use of decision theory. However, the development of VentPlan has stopped and it will not be discussed further, but it should be noted that several of the qualities of INVENT discussed in the following were also qualities of the VentPlan system.

To the best of my knowledge, the prospective evaluation of INVENT presented in paper III is the first prospective evaluation of a model-based medical decision support system for ventilator management since the studies with the OPTPROG system by Rudowski et al. in the early nineties [69,70]. OPTPROG was prospectively evaluated for suggestions on f, Vt and PEEP, which represent a more complex problem than management of FiO_2. However, OPTPROG had several issues which likely would prevent routine clinical use. OPTPROG was based on linear models with model parameters having no physiological interpretation. As such the users would have little extra to gain from using this system compared to a rule-based system, except the potential of preventing trial and error when selecting therapy. Despite the simple model, the parameter estimation procedure took approximately one hour and required four arterial blood gas measurements [69,70], a frequency of arterial blood sampling in excess of that normally used in clinical practice. Rudowski et al. argued that when enough patient data was accumulated, statistical analysis could be used to acquire a priori knowledge of model parameters potentially simplifying or obviating the parameter estimation procedure [69]. However, the heterogeneity of ALI/ARDS patients reported in clinical studies strongly contradicts this [e.g. 36,37].

The SIVA system [72] is based on a two parameter physiological model of gas exchange to simulate patient response to changes in FiO_2, and empirical models to simulate patient response to changes in respiratory frequency and inspiratory pressure [72]. The two parameters of the gas exchange model have a physiological interpretation [75], however, the authors stated that estimation of model parameters requires a pulmonary artery catheter and that there were convergence problems. As such, the authors suggested that for prospective use, shunt should be estimated using a fuzzy inference system [62] and physiological dead space had to be estimated by the clinician [72]. The parameter estimation is therefore limited to requiring an arterial

blood gas sample at a single level of FiO_2. The system has at present only been evaluated using model simulations, preventing any conclusions on the accuracy of model predictions.

The FLEX system uses several simple models to describe patient response to changes in FiO_2, PEEP, f and I:E-ratio [74]. All the models implemented in FLEX are either very simple without any model parameters or empirical having parameters without a physiological interpretation. These empirical model parameters are not tuned to describe the individual patient. The simple nature of the models used in FLEX allows the system to be used from measurements readily available at the bedside in the ICU, however, this also prevents FLEX from providing the clinician with a deeper physiological understanding of the patient.

FLEX incorporates scalability such that if certain measurements are not available the system uses a different, i.e. simpler, approach to calculate suggestions. This can be a valuable quality of the system, especially when used outside the ICU where measurements of lung status are sparse. The different methods used in this PhD project (see section 2.2) illustrate that the parameter estimation procedure used for the gas exchange model in INVENT is to some extent scalable. In addition it has been shown that in patients with cardiac incompensation the parameters can be estimated without an arterial blood gas measurement using default values [123]. However, it would still be necessary to measure variation in oxygenation with varying FiO_2 to separate the effects of shunt and $\dot{V}A/Q$ mismatch.

Both SIVA and FLEX are hybrid systems using models in combination with rules to calculate suggestions on changes in therapy. As such these systems, like rule-based systems, do not make it obvious to the clinician what compromises have been made by the system.

4.4 Future work

The version of INVENT originally presented by Rees et al. in 2006 was intended for decision support of not only FiO_2 but also of Vt and f [73]. In the following, the relevance of providing decision support on these settings is discussed as well as the

future work necessary to enable prospective evaluation of INVENT for suggesting FiO_2, Vt and f in an ICU. Thereafter it is discussed what future work may allow INVENT to provide suggestions on PEEP, for which the appropriate levels remains elusive. Finally this section will address the necessary work required to facilitate future clinical integration of INVENT.

Advice on FiO_2, Vt, and f

A recent epidemiological study by Esteban et al. showed that tidal volumes in general have been decreased in ARDS patients in clinical practice, but also that this has not reduced mortality more than 5 percent since 1998 [124] and ICU and hospital mortality in ARDS patients remain above 50% and 60%, respectively [124]. Several reasons may have contributed to this apparently high mortality in comparison with those of the multicenter clinical trials reporting mortalities below 30% [e.g. 28,30]: the studied populations may have been more heterogeneous; the design of the retrospective study by Esteban et al.; change in composition of patients presenting in the ICU; or perhaps the difficulty for clinicians to use the guidelines in clinical practice for the benefit of individual patients? Use of a DSS could potentially help to standardize care according to the individual patient.

INVENT has been shown retrospectively to provide appropriate suggestions of FiO_2, Vt and f in cardiac surgery patients mechanically ventilated in an ICU [125]. In these patients the two parameter gas exchange model was successfully used to describe the pulmonary gas exchange of O_2 and CO_2. However, the results presented in paper IV illustrate that a three parameter model is necessary to describe both O_2 and CO_2 gas exchange in intensive care patients. As such, this model must be implemented in INVENT before an eventual retrospective or prospective evaluation in intensive care patients. This will require a measurement of end-tidal fraction of CO_2 in addition to the measurements used for estimating model parameters to describe O_2 gas exchange.
Paper IV was limited to compare minimal models in intensive care patients representing some of the most complex respiratory failure patients with regards to gas exchange. The two parameter model may be sufficient to describe gas exchange of both O_2 and CO_2 in “simpler” patients, as shown in cardiac surgery patients by Allerød et al. [125].

Currently, INVENT uses a single set of penalty functions to calculate suggestions, regardless of patient type and clinical circumstances. Although the majority of changes in FiO_2 have been appropriate and all have been safe, results in a few patients indicate that INVENT may be too prone to increase FiO_2 from low levels when SaO_2 is sufficient (see patient illustrated with dots in Figure 16). It may be sufficient to remove this tendency by making ischemia penalties smaller at SaO_2 above 0.97 or toxicity penalty a little higher at low FiO_2 (see Figure 7). Alternatively a new set of penalties could be formulated for example for weaning patients. In all circumstances, a new set of penalties would be relevant for patients with severe chronic obstructive pulmonary disease, where the patient's normal levels of oxygenation may be reduced.

Some additional modifications of INVENT are necessary before a prospective evaluation can be performed for the three settings. The current simple model of lung mechanics implemented in INVENT assumes a constant linear compliance relating tidal volume to the difference between peak pressure and PEEP. Changes in tidal volume can, however, affect lung status, e.g. increases in tidal volume may increase peak pressure potentially recruiting collapsed alveoli reducing shunt thereby leading to less accurate predictions using the gas exchange model. As described in the following section on PEEP advice, it is difficult to formulate a mathematical model of lung mechanics, which is able to describe lung mechanics of patients from clinical data. Therefore it may be necessary to resort to a trial and error approach as in rule-based systems. This can be performed by implementing a step to target algorithm in INVENT such that large changes in tidal volume can be performed in steps and gas exchange can be evaluated at each step. Similarly increases in f may cause intrinsic PEEP. As such, the step to target functionality should include f, and end-expiratory occlusions should be performed allowing quantification of intrinsic PEEP.

Advice on PEEP

The large number of clinical trials which have failed at finding an optimal PEEP strategy in ALI/ARDS patients [e.g. 29,31,32] illustrate the need for better understanding of how PEEP should be managed. An important reason may be the lack of understanding of how changes in PEEP affect lung mechanics as well as gas exchange. Physiological models have been constructed to describe lung mechanics

either addressing specific components of the respiratory system in great detail [e.g. 126] or the complete respiratory system using an empirical approach [127]. Whilst these models have added to the current understanding of lung mechanics they have not provided a fundamental understanding of the mechanical effects of changes in PEEP. In addition, attempts to link lung mechanics and gas exchange have been few [128], despite the fact that securing gas exchange is one of the goals of changes in PEEP.

In order to enable model-based decision support of PEEP a novel model must be constructed, capable of explaining the effects of changes in PEEP. The model should be able to describe the effect of PEEP on both ventilation and perfusion, thereby allowing also description of gas exchange.

To describe ventilation, the model should include the contributions of: the hydrostatic gradient down the lung due to the weight of the lung [4]; the chest wall; the lung tissue; and pulmonary surfactant. The chest wall and pulmonary surfactant have often been neglected in models of lung mechanics. The chest wall has been suggested as important in understanding recruitments maneuvers in ALI/ARDS patients [129]. Pulmonary surfactant is considered vital for mechanical stability during breathing [130], and inhibition of surfactant due to mechanical ventilation and edematous fluid entry indicate the importance of understanding surfactant to understand lung mechanics in respiratory disease [18]. Work has begun describing the different components in the healthy lungs [131], however future work is required addressing how the properties of the different components of the respiratory system change in respiratory disease.

To the best of my knowledge, no mathematical models have been built to describe how changes in ventilatory pressures affect the distribution of pulmonary perfusion. We have begun building a model with this aim [132]. The model at its current state, describes the pulmonary perfusion in the healthy human lungs and is able to describe experimentally measured total capillary perfusion, volume and surface area [132]. Future work is required for describing pulmonary perfusion in respiratory diseases including addition of hypoxic pulmonary vasoconstriction, which acts to reduce pulmonary perfusion in hypoxic lung regions [133].

In addition to modeling the different components of the respiratory system, the heterogeneity of the lungs must be considered. A possible solution is to build stratified models allowing different layers to have different properties, e.g. due to different pleural pressures as caused by a hydrostatic gradient [4]. This may enable such models to describe the 'baby-lung' of ARDS, that is, a very small volume of lung being ventilated due to the remaining lung being collapsed, or consolidated [5]. Models of lung mechanics have been built using a stratified structure including the model by Steimle et al. [127,128,131,134]. The model of perfusion introduced by Mogensen et al. [133] is based on the same stratified structure as the model by Steimle et al. [134], illustrating the possible combination of these models in the future to describe gas exchange and thereby also the link between lung mechanics and gas exchange.

Alternatively to modeling the effects of changes in PEEP, one may derive simple algorithms describing compromises considering changes in FiO_2 versus PEEP as done in clinical trials [e.g. 28]. However, changes in PEEP will likely impact the patient's gas exchange status and should as such be followed by a re-estimation of parameters of the gas exchange model. This may introduce the need for trial and error in some patients, similar to that necessary in rule-based systems.

Clinical integration

Whilst a DSS may provide sound advice, provide physiological understanding and in general improve patient care, it is of no value if it is not used at the bedside. An obvious way to enable successful clinical integration is through commercial collaboration with companies producing mechanical ventilators. This has been demonstrated with the GANESH system originally presented by Dojat et al. [49], which is now implemented as part of the SmartCare™ system by Dräger Medical [64]. Besides performing several large studies demonstrating the efficiency of the system, as performed with GANESH [51-53], INVENT could benefit significantly from collaboration with the industry. However, as long as data can be retrieved from the ventilator, a system as INVENT could potentially be developed as a stand-alone system, albeit this would introduce significant obstacles, the main being that it would

be difficult if not impossible to make the system or parts of the system such as parameter estimation, closed loop.

Morris described in 2000 several barriers to the use of computerized clinical protocols, i.e. rule-based DSSs [40]. The list presented by Morris included a lot of barriers concerning clinical culture and fear of losing authority. However, several barriers addressed qualities of the DSS, which would apply for an eventual integration of INVENT as well. These barriers can be translated to a few qualities a DSS should have: The system should not add more burdens to the already stressed critical care staff either in form of excessive data entry or high complexity; the system should be usable in a large variation of clinical cases not just the most prevalent; and the system should be supported by a technological infrastructure such as electronic patient records.

As discussed previously the parameter estimation procedure used for estimating parameters of the gas exchange model in INVENT does not add considerable burden to the clinical staff, and it could potentially be automated. Further automation could include automatic detection of when new parameter estimation is necessary, e.g. after changes in settings or posture. When estimated, model parameters act to reduce complexity integrating data from various devices, and providing a physiological understanding of the patient directly related to changes in therapy.

Paper III showed that INVENT could provide decision support of FiO_2 in patients with different severities of lung disorder and in controlled as well as spontaneous ventilator modes. The current version of INVENT for providing suggestions of Vt and f is limited to volume controlled mode. Inclusion of more complex models of lung mechanics and respiratory drive would potentially allow INVENT to provide decision support in patients ventilated in pressure control mode as well as support ventilator modes. Models of respiratory drive have been built, which potentially could be used for such application [e.g. 135,136].

INVENT is implemented in the database system ICARE [118], which can facilitate automatic retrieval and storage of measurement data from several medical devices. In addition calculated values, estimated model parameters and INVENT advice can be

stored in the database, and values not automatically retrieved may be input manually. As such ICARE provides a technological infrastructure supporting all tasks related to using INVENT. Integration of ICARE with existing clinical databases would further strengthen this technological infrastructure, perhaps similar to the HELP database used in the successful Salt-Lake city protocols [45-48].

4.5 Model limitations

A number of assumptions and simplifications have been made in the project regarding the use of minimal models to describe pulmonary gas exchange and when estimating model parameters. These are discussed in the following.

All minimal models used in this PhD project have assumed continuous ventilation and perfusion, steady state, and that end-tidal gas and mixed alveolar gas fractions are equal. These assumptions do not represent the true nature of human breathing, which is tidal [137]. Models of gas exchange have been built describing tidal ventilation [e.g. 138,139]. However, estimation of model parameters for these models using clinical data has so far not been demonstrated, and the models have either been limited to simulations studies [138] or parameters have been estimated using a combination of MIGET and multiple breath nitrogen washout measurements [139]. As such, minimal models as those presented here, appear currently to represent the most accurate descriptions of gas exchange from clinical data.

Effects of diffusion limitations have not been included in the models. Diffusion limitation has a similar effect on pulmonary gas exchange as $\dot{V}A/Q$ causing a ΔPO_2 [140]. Studies with MIGET, however, has demonstrated that in the majority of patients, $\dot{V}A/Q$ mismatch is likely a better description of physiology [93,93,140] except in cases of pulmonary fibrosis [93], exercise [141] or mild exercise during hypoxia [141,142].

The parameter estimation procedure depends on measurement of arterial oxygenation at steady state at varying levels of FiO_2. This is done under the assumption, that varying FiO_2 does not alter the physiology of the patient in such a way that $\dot{V}A/Q$ mismatch and shunt are affected significantly. Variation in FiO_2 may affect

lung physiology through absorption atelectasis and hypoxic pulmonary vasoconstriction (HPV). Absorption atelectasis is not likely to have an impact on parameter estimation, as it has been shown during induction of anaesthesia that absorption atelectasis mainly occurs at FiO_2 levels of 0.8 or more [20], whilst parameter estimation rarely requires FiO_2 levels as high as 0.8. HPV reported effects on gas exchange have been moderate [143] or considerable [144], but has represented maximal responses to changes in FiO_2, the expected changes with the smaller variations in FiO_2 being less likely to significantly affect pulmonary gas exchange. Studies with MIGET [145,146] and computer simulations [147,148] have also shown small changes in model parameters with large variations in FiO_2.

VDana and Q were assumed constant during the parameter estimation procedure, see section 2.2. In paper I, VDana and Q from the original papers were used [102-104]. In papers II and IV VDana was measured. In paper III, VDana including apparatus dead space was assumed to be 0.2 l in all patients. As VDana varies with posture, body size etc. [77], this simplification may have affected the correctness of estimated model parameters. However, it would have no consequence on INVENT suggestions of FiO_2, as they would be based on model fits to measured $FetO_2$-SpO_2 curves and as such would reflect patient status as long as the model fitted data well.
In papers II-IV, Q was either measured or estimated from body surface area and a population characteristic CI. This may likely not have reflected the true Q in some patients. However, a previous study with a two parameter model describing shunt and diffusion limitation, i.e. a ΔPO_2, based on mass conservation and the same assumptions as models used in this project, showed that parameter estimation was insensitive to moderate variations in Q [106], with changes in Q of 40% changing fs by 0.04 and ΔPO_2 by 0.5 kPa.

4.6 Clinical perspectives

The results presented in this thesis illustrate that a model-based DSS for mechanical ventilation may help to standardize therapy according to the individual patient. A model-based DSS may also help to diminish information overload, which if unattended affects clinical decision making [38,40]. INVENT uses a gas exchange model to integrate information from ventilator settings, hemodynamic parameters, oxygenation, acid base chemistry of blood and metabolism into two model

parameters, shunt and fA2 (ΔPO_2) describing the gas exchange status of the patient. This can be valuable in the difficult to manage patients. In the easily managed patients, a model-based DSS as INVENT may free the focus of the clinicians on more challenging therapy.

Results in papers I and IV illustrate that several measurements currently used in clinical practice are insufficient to provide an accurate description of pulmonary gas exchange in intensive care patients including ALI/ARDS patients. Results in paper I illustrated how the PaO_2/FiO_2 ratio varies with changes in FiO_2 and SaO_2. The PaO_2/FiO_2 ratio is the hypoxemia index used in the definition of ALI/ARDS and constitutes the single value separating ALI and ARDS diagnosis [1]. Paper I showed several patients changing disease classification due to variation in FiO_2, a common therapeutical intervention normally not affecting pulmonary gas exchange. Other theoretical studies have come to similar conclusions but without involving clinically measured variations in the PaO_2/FiO_2 ratio [149-151].

So how should the refractory hypoxemia evident in ALI/ARDS patients be defined? As suggested in paper I, at least the FiO_2 level should be informed when using the PaO_2/FiO_2 ratio, however also SaO_2 has an impact and would be appropriate to inform. However, standardizing FiO_2 when including patients is unpractical and standardizing both FiO_2 and SaO_2 is even more so due to the varying severities of lung disorder seen in ALI/ARDS. Alternatively, minimal models of gas exchange could be used by estimating model parameters and classifying hypoxemia according to the levels of shunt and degree of $\dot{V}A/Q$ mismatch. The ability of the three parameter model to describe large fractions of shunt and large perfusions going to regions with low $\dot{V}A/Q$ ratios as shown in studies using MIGET indicate that the three parameter model may be suitable for this application.

It has also been argued that a future hypoxemia index used in ALI/ARDS definition should not vary with changes in PEEP [152]. We disagree with this approach, as changes in PEEP, unlike most changes in FiO_2, affect the pulmonary physiology [94,95] and may have different effects in different patients [37]. However, standardization of the level of PEEP used when evaluating patients could be very

relevant to potentially separate patients whose alveoli are readily recruited and where PEEP may keep these alveoli open from patients with consolidated lung regions. This is in line with several other authors advocating use of standardized ventilator settings when enrolling ALI/ARDS patients for clinical trials [153-154].

5. General Conclusions

1. A two parameter model of pulmonary gas exchange describing intrapulmonary shunt and ventilation-perfusion mismatch can describe variation in oxygenation with changes in FiO_2. The shunt only model can not describe this variation accurately.
2. The PaO_2/FiO_2 ratio varies significantly with FiO_2 and its use as a hypoxemia index is questionable. As a minimum requirement measurements of PaO_2/FiO_2 should be accompanied by the corresponding FiO_2 level.
3. The INVENT system provides appropriate suggestions of FiO_2 and SaO_2 in intensive care patients.
4. Compared to attending clinicians INVENT standardizes the FiO_2 levels and values of SaO_2 according to the individual patient.
5. All suggestions of FiO_2 provided by INVENT results in safe values of SaO_2.
6. When identified, the two parameter gas exchange model describing shunt and ventilation-perfusion mismatch is capable of predicting the oxygenation response of intensive care patients to changes in inspired oxygen.
7. A three parameter model is necessary for an accurate minimal model representation of the pulmonary gas exchange of both O_2 and CO_2 in intensive care patients.
8. Estimation of model parameters for a three parameter model describing shunt and ventilation-perfusion mismatch may be performed using routine clinical data, potentially allowing this model to be used at the bedside in an ICU and as part of INVENT for providing advice on tidal volume and respiratory frequency.

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Summary

Mechanical ventilation is one of the key life-sustaining therapies applied in the intensive care unit. Management of mechanical ventilation is a complex task due to conflicting clinical goals. Decision support systems provide a tool for clinicians when selecting therapy by providing patient specific suggestions on therapy. This PhD thesis addresses the use of minimal models of pulmonary gas exchange, comparing models of varying complexity and clinically available measurements, and the use of a minimal model of O_2 gas exchange in a decision support system to provide suggestions on inspired O_2 in intensive care patients.

The thesis describes the clinical and technical backgrounds of the project. Acute lung injury and acute respiratory distress syndrome (ALI/ARDS) are described constituting some of the most complex diseases with regards to mechanical ventilation, with lungs being susceptible to ventilator induced lung injury (VILI). Different VILI types are described as well as major clinical trials with lung protective ventilator strategies. The review illustrates that controversy exists and the optimal therapy for the individual patient remains elusive. Whilst volumes and pressures are the focus of current strategies, levels of inspired O_2 are rightfully not ignored and minimized in the majority of trials. Decision support systems for mechanical ventilation are reviewed illustrating the predominate role of rule-based systems. Two inherent weaknesses of these systems are brought forward. Rule-based systems do not provide a deeper physiological understanding of the patient nor the provided advice, and may require trial and error to find appropriate therapy. Model-based systems may solve both these problems using mathematical models with parameters having a physiological interpretation. Finally pulmonary gas exchange models are reviewed arguing that currently available measurements and models in clinical practice are oversimplified as they vary with therapies not affecting physiology. The reference technique for measuring gas exchange, the multiple inert gas elimination technique, is too complex for clinical application. Existing minimal models of pulmonary gas exchange represent compromises between complexity and feasibility.

Four studies were carried out resulting in four corresponding papers forming the basis for this thesis. Models of different complexities were used, but all being based on

conservation of mass, continuous breathing and perfusion and assuming steady state. An existing model of the acid base chemistry of blood was implemented in the models to describe the gas exchange of both O_2 and CO_2. Parameter estimation methods were tailored to the varying aims and available data for the four studies.

Paper I shows retrospectively that the predominant hypoxemia index, the PaO_2/FiO_2 ratio, varies significantly with changes in inspired O_2 in various patient groups including intensive care patients. A one parameter model describing intrapulmonary shunt can not describe this variation but a two parameter model describing shunt and ventilation/perfusion mismatch can.

Paper II presents use of this two parameter model in the decision support system INVENT as part of a retrospective evaluation of INVENT in intensive care patients. INVENT provided appropriate suggestions of inspired O_2 and model simulated levels of oxygenation in comparison to levels used in clinical practice.

Paper III describes a prospective study comparing INVENT suggested levels of inspired O_2 and resulting measured arterial oxygen saturation with levels selected by attending clinicians in an intensive care unit. INVENT provided appropriate suggestions on inspired O_2 compared to attending clinicians.

Paper IV describes a retrospective study of the necessary minimal model complexity to accurately describe pulmonary gas exchange of both O_2 and CO_2 in intensive care patients. A three parameter model was shown to be necessary. This model was able to describe perfusion of lung units with very low ventilation/perfusion ratios, a characteristic shown in ALI/ARDS patients using the multiple inert gas elimination technique.

In conclusion, results presented in this thesis show that minimal models provide a more accurate description of gas exchange than measurements currently available in clinical practice. When used in a decision support system, minimal models also enable predictions of changes in oxygen saturation upon changes in inspired O_2 fraction. The INVENT decision support system using a two parameter minimal model of O_2 gas exchange provides appropriate suggestions on inspired O_2 fraction in intensive care patients in comparison to attending clinicians, potentially standardizing care according to the individual patient. Inclusion of a three parameter minimal model of O_2 and CO_2 gas exchange may allow INVENT to provide appropriate suggestions on inspired O_2, tidal volume and respiratory frequency.

Danish summary

Mekanisk ventilation er en af de primære livreddende terapiformer i anvendelse på en intensivafdeling. Modstridende kliniske mål komplicerer indstilling af en respirator. Beslutningsstøttesystemer udgør et muligt værktøj til at hjælpe læger med valg af den mest hensigtsmæssige terapi. Denne PhD-afhandling omhandler brugen af minimal-modeller af den pulmonære gasudveksling. Under projektet er minimal-modeller med forskellige grader af kompleksitet samt klinisk tilgængelige måleteknikker for evaluering af gasudveksling blevet sammenlignet, og en minimal-model af O_2 gasudveksling er blevet anvendt i et beslutningsstøttesystem til rådgivning om den inspirerede iltfraktion ved patienter på en intensivafdeling.

Som udgangspunkt beskrives projektets kliniske og teknologiske baggrunde. Akut lungeskade og akut respiratorisk distress syndrome (ALI/ARDS) beskrives, idet de udgør komplekse former for respiratorisk svigt og patienterne er kendetegnet ved at være tilbøjelige til at udvikle respiratorinduceret lungeskade (ventilator induced lung injury - VILI). Der redegøres for forskellige VILI typer samt vigtige kliniske studier i strategier for mekanisk ventilation. Redegørelsen viser, at der er kontroverser omkring hvad VILI er, og hvordan strategier for mekanisk ventilation bedst muligt tilrettelægges for den individuelle patient. De fleste studier har fokus på volumen og tryk, men den inspirerede iltfraktion er med rette ikke blevet ignoreret og søges minimeret i størstedelen. En redegørelse for udviklingen indenfor beslutningsstøttesystemer gør det klart, at regel-baserede systemer dominerer. Der er dog to grundlæggende svagheder ved regel-baserede systemer. De giver ikke en forståelse for patientens fysiologi eller rådene de tilbyder, og de kan kræve, at man prøver sig frem for at finde den mest hensigtsmæssige terapi. Model-baserede systemer kan potentielt løse begge problemer ved brug af matematiske modeller med parametre tilknyttet en fysiologisk fortolkning. Til slut redegøres for matematiske modeller af den pulmonære gasudveksling. Her argumenteres for, at tilgængelige målinger af gasudveksling i klinisk praksis er for simple, idet de varierer med terapiændringer, der ikke påvirker patientens fysiologi. Referenceteknikken, the multiple inert gas elimination technique (MIGET) er for kompleks til klinisk brug. Minimal-modeller udgør et kompromis imellem kompleksitet og anvendelighed.

Afhandlingen er baseret på fire artikler. Minimal-modeller af forskellig kompleksitet er blevet anvendt, men alle er baseret på massebevarelse, kontinuert vejrtrækning og perfusion og antager ligevægtstilstand. En eksisterende model af blodets syre-base kemi blev implementeret i modellerne for at kunne beskrive gasudveksling af både O_2 og CO_2. Metoder til parameterestimering blev tilpasset til tilgængelige data og de enkelte artiklers formål.

Artikel I viser retrospektivt, at det dominerende hypoksæmi-index, PaO_2/FiO_2, varierer signifikant med ændringer i den inspirerede iltfraktion. En en-parameter model af intrapulmonær shunt kunne ikke beskrive denne variation i modsætning til en to-parameter minimal-model af shunt og ventilation/perfusions misforhold.

Artikel II beskriver brug af den samme to-parameter model i beslutningsstøttesystemet INVENT, som blev retrospektivet evalueret i patienter på en intensivafdeling. INVENTs råd om inspireret iltfraktion og model-simulerede arterielle iltmætninger var hensigtsmæssige i sammenligning med klinisk praksis.

Artikel III beskriver et prospektiv studie på en intensivafdeling, som sammenlignede INVENTs råd om inspireret iltfraktion og de målte resulterende arterielle iltmætninger med niveauer valgt af vagthavende læger. INVENTs råd var hensigtsmæssige i sammenligning med lægernes.

Artikel IV beskriver en retrospektiv undersøgelse af den nødvendige minimal-model kompleksitet for at beskrive den pulmonære gasudveksling af både O_2 og CO_2 i patienter på en intensivafdeling. Studiet viste, at en tre-parameter model er nødvendig. Denne model kan beskrive perfusion af lungeenheder med meget lav ventilation/perfusions ratio, hvilket tidligere er beskrevet i ALI/ARDS patienter med MIGET.

Resultaterne præsenteret i denne afhandling viser, at minimal-modeller giver en mere nøjagtig beskrivelse af gasudveksling end tilgængelige målinger i klinisk praksis. I beslutningsstøttesystemer kan disse modeller anvendes til at simulere ændring i arteriel iltmætning ved ændringer i inspireret iltfraktion. INVENT har ved brug af en minimal-model givet hensigtsmæssige råd om inspireret iltfraktion i forhold til vagthavende læger på en intensivafdeling. Potentielt kunne systemet standardisere, hvordan inspireret iltfraktion indstilles i forhold til den specifikke patient. Inklusion af en tre-parameter minimal-model kan muliggøre at INVENT i fremtiden også kan rådgive om tidalvolumen og respirationsfrekvens på en intensivafdeling.