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DENMARK

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by

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ENGLISH SUMMARY

Selecting the level of ventilator support is difficult, with patients responding in different ways to reduction or increase of support. Providing adequate level of support is necessary to avoid over-assistance and the risk of inducing ventilator induced lung injuries (VILI), while avoiding respiratory distress or respiratory muscle failure. This thesis described previous clinical and technological solutions to assist physicians in selecting the adequate level of support. These solutions have focused on guidelines or rule-based systems to set ventilator support. A few technological solutions have integrated physiological models to describe patients' response to changes in mechanical ventilation, allowing simulation of patient response. One of these is INVENT, which integrates models of pulmonary gas-exchange, blood acid-base and oxygenation status, body buffering, and lung mechanics. INVENT describes patients in controlled ventilation modes, which represents a limitation as the majority of patients are ventilated in assisted ventilation modes. The aim of this PhD thesis is to integrate a model of respiratory control into the set of models included in the INVENT system in order to enable description of patients in assisted ventilation modes i.e. spontaneously breathing patients, on changes in the level of ventilator support.

The thesis reviews the appropriate models for inclusion in INVENT, verifying that they have the correct level of abstraction to allow bedside use, and a model of respiratory control is selected. This model is described, and integrated into the set of models included in INVENT. To adequately integrate the model of respiratory control, the model was modified to allow calibration and simulate down-regulation of ventilation. Two additional models were included to quantify muscle function and effective compliance.

A sensitivity analysis is performed to examine the behavior of the respiratory control model and identify potential patient-specific model parameters, and a method of parameter estimation presented. The models of INVENT including the respiratory control model are then evaluated prospectively in two clinical protocols including patients ventilated in assisted controlled ventilation (ACV), and pressure support ventilation (PSV). These clinical studies evaluated the models ability to describe patient response to 5 different levels of tidal volume or pressure support. Model simulated values of respiratory frequency (fR), arterial pH (pHa), and end-tidal CO_2 ($FECO_2$) compared well with measured values, giving low bias and narrow limits of agreement.

In summary, this PhD thesis presents a set of models which allows the description and simulation of patients' response to changes in the level of

ventilator support. Two prospective clinical studies showed that it is possible to describe and simulate patients' response to changes in ventilator support.

DANSK RESUME

Det er svært at vælge niveauet af respiratorstøtte, da patienter kan reagere forskelligt på sænkning eller øgning i støtte. Det er nødvendigt at give det rette niveau af støtte for at mindske risici for over-støtte og respiratorinduceret lunge skade (ventilator induced lun ginjury - VILI) men i modsat fald også undgå besvært med vejtrækningen og udmattelse af de respiratoriske muskler. Denne PhD-afhandling beskriver tidligere kliniske og teknologiske løsninger til at støtte læger i at vælge hensigtsmæssig respiratorstøtte. Disse løsninger har fokuseret på guidelines eller regelbaserede systemer til at indstille respiratorstøtte. Enkelte teknologiske løsninger har integreret fysiologiske modeller med det formål at beskrive patienters reaktion på ændringer i respiratorindstillinger og hermed muliggjort at patienters reaktion kan simuleres. Et af disse systemer er INVENT, som integrerer modeller af pulmonær gasudveksling, blodets syre-base kemi og iltning, kroppens bufferegenskaber, og det respiratoriske systems mekaniske egenskaber. INVENT kan beskrive patienter der ventileres i et kontrolleret ventilationsmodus. Dette udgør en begrænsning for systemet, da flertallet af patienter ventileres i et støttet ventilationsmodus. Målet med denne PhD-afhandling er at integrere en model af respiratorisk kontrol med de eksisterende modeller i INVENT for at muliggøre en beskrivelse af patienter i støtte ventilationsmodi, det vil sige patienter som har spontan respiration, ved ændring i respiratorstøtte.

PhD-afhandlingen redegør for egnede modellers inklusion i INVENT, verificerer at modellerne har det rette abstraktionsniveau der muliggør praktisk klinisk brug, og en model af respiratorisk kontrol udvælges. Denne model beskrives og integreres med de eksisterende modeller i INVENT. For at kunne integrere modellen hensigtsmæssigt med de eksisterende, er modellen blevet modificeret så den kan kalibreres og simulere sænkning af ventilation. To yderligere modeller er blevet inkluderet til at kvantificere respiratorisk muskelfunktion og effektiv lungeeftergivelighed.

I PhD-studiet udføres en sensitivitetsanalyse som undersøger modellen af respiratorisk kontrol og identificerer potentielle patientspecifikke modelparametre og en metode til estimering af modelparametre udvikles. Efterfølgende evalueres INVENTs modeller inklusive modellen af

respiratorisk kontrol prospektivt i to kliniske protokoller som inkluderer patienter i assisted controlled ventilation (ACV) og pressure support ventilation (PSV). Disse klniske studier evaluerer modellernes evne til at beskrive patienters reaktion på 5 forskellige niveauer af åndedrætsvolumen eller trykstøtte. Modellernes simulerede værdier af åndredrætsfrekvens (fR), arteriel pH (pHa) og slutekspiratorisk CO_2 fraktion ($FECO_2$) er sammenlignelige med målte værdier med resulterende små bias og snævre limits of agreement.

Kort opsummeret præsenterer denne PhD-afhandling et sæt af modeller som muliggør beskrivelse og simulation af patienters reaktion på ændringer i iveau af respiratorstøtte. To prospektive kliniske studier viste at det er muligt at beskrive og simulere patienters reaktion på ændringer i respiratorstøtte.

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CHAPTER 1. CLINICAL AND TECHNICAL BACKGROUND

1.1. INTRODUCTION

Mechanical ventilation is a life-sustaining therapy for patients residing in intensive care. It is used to reduce the work required to breathe, to promote CO_2 removal, and to aid in O_2 delivery to the tissues, maintaining adequate blood acid-base and oxygenation status. There are two major modes of mechanical ventilation, control and assisted, with the difference between these depending upon patients' ability to initiate a breath. In controlled modes of ventilation, breaths are primarily triggered by the ventilator and not the patient. This means that the patients' respiratory frequency is decided by the physician and set on the ventilator along with inspired oxygen and either ventilator volume or pressure. In contrast, in assisted modes, breaths are primarily triggered by patient effort. As a result, patients decide their own respiratory frequency with the physician deciding the appropriate level of inspired oxygen and either volume or pressure support.

Selecting the appropriate settings for mechanical ventilation is a difficult process. Patients' are highly heterogeneous and have different abnormalities in various physiological systems including pulmonary gas-exchange, blood acid-base, respiratory drive, metabolism, and circulation. Optimizing mechanical ventilation requires understanding of the individual patient's physiological state. To aid in this process, physiological models of numerous of these physiological systems have been included in a decision support system (DSS) to advice upon appropriate mechanical ventilation (1). This set of physiological models was shown to describe patient response to changes in ventilation (2-5), but the models included in these systems have limited application. The system can only describe patients in controlled ventilation modes (6). Since the majority of patients on mechanical ventilation are in assisted ventilation modes, this represents a real limitation (7-10).

Describing patients in assisted ventilation is more complex than describing controlled ventilation. During assisted ventilation, patients are spontaneously breathing, which is a physiological process that involves additional physiological systems (e.g. respiratory chemoreflex, cerebrospinal fluid acid-base status). Models describing spontaneous breathing, i.e. respiratory control, have been used to describe the respiratory response of subjects to

hypoxia and hypercapnia following induced abnormalities in blood acid-base status (11-13). It may therefore be possible to integrate a model of respiratory control into the above mentioned set of physiological models and in doing so help provide a description of patients in assisted ventilator modes. The aim of this PhD thesis is to improve a set of physiological models, in order to add the functionality necessary to describe patients ventilated in assisted ventilation modes. To do so, the physiological models are required to be complex enough to capture patients' response to changes in the level of ventilator support, while at the same time being simple enough to be tunable to the individual patient at the bedside. The selection of appropriate models is therefore not trivial, and this thesis describes the selection criteria of appropriate models of respiratory control. The respiratory control model that best meets the selection criteria is selected and integrated into the set of physiological models. This integrated set of models is then prospectively evaluated in patients on mechanical ventilation in assisted ventilation modes, at different levels of ventilator support.

1.2. DESCRIPTION OF THE MAJOR VENTILATOR MODES

The primary objectives of mechanical ventilation are to unload the respiratory muscles, and promote removal of CO_2 and delivery of O_2, keeping adequate blood acid-base and oxygenation status. To meet these objectives, selection of appropriate ventilator settings is necessary. This process starts with selection of the ventilation mode, which depends upon patients' state of consciousness. In passive patients (i.e. heavily sedated or/and paralyzed), the ventilator takes over the respiratory muscles' workload, as patients cannot generate spontaneous breathing effort. In active patients (i.e. awake or slightly sedated), the ventilator may unload the respiratory muscles with patients generating spontaneously breathing effort. This section describes general aspects of controlled and assisted ventilation modes. The two most common assisted ventilation modes are explained, as these modes are used during the clinical studies performed as part of this PhD thesis.

1.2.1. CONTROLLED VENTILATION MODES

During controlled ventilation modes the ventilator delivery of breaths is typically triggered mechanically by the ventilator, with the expiratory phase of the respiratory cycle relying on the elastic recoil of the respiratory system rather than patient effort. In general, there are two main controlled ventilation modes, defined upon the variable that the ventilator controls. In volume control, the ventilator controls the inspiratory tidal volume (VT), and in pressure control, the ventilator controls the inspiratory pressure (Pinsp). The relationship between the volume and/or pressure delivered depends on the

mechanical characteristics of the respiratory system (i.e. resistance and compliance) (14,15). The following ventilator settings are set by physicians during controlled ventilation modes: ventilation controlled variable, VT or Pinsp; inspired fraction of oxygen (FIO_2); respiratory frequency (fR), which is the number of mechanically delivered breaths provided to the patient per minute; the inspiratory time (Ti), which is the time required to achieve VT according to the set inspiratory flow during volume-controlled ventilation, or is the time Pinsp is maintained during pressure controlled ventilation; inspiratory flow ($\dot{V}i$), is set in volume-controlled ventilation, and is the inspiratory flow delivered to the patient, its value depends on VT and Ti; ramp or slope, is set on pressure-controlled ventilation, and is the time it takes to the ventilator to pressurize the patient breathing circuit to reach Pinsp; inspiratory flow pattern, defines the shape of the flow profile provided to the patient, which can be either accelerating, decelerating, or constant, depending on the flow setting for volume-controlled ventilation or ramp time setting for pressure-controlled ventilation; and level of positive end expiratory pressure (PEEP).

In volume-controlled ventilation mode, physicians determine the minute ventilation ($\dot{V}E$) i.e. the product between VT and fR, a known value of $\dot{V}E$ is therefore guaranteed in this mode. In contrast, during pressure controlled ventilation, a predefined $\dot{V}E$ is not known, and $\dot{V}E$ can change acutely due to a sudden change in lung compliance. A fixed $\dot{V}E$ can be seen as an advantage of volume-controlled mode, however, pressure-controlled ventilation is usually associated with both a lower Pinsp and a decelerating flow pattern on inspiration. Both of these are thought to be beneficial and have led to combined pressure and volume modes such as pressure regulated volume controlled (PRVC) which combine the benefits of pressure control with a guaranteed $\dot{V}E$ (16).

1.2.2. ASSISTED VENTILATION MODES

During assisted (or assisted/supported) ventilation modes the ventilator delivery of breaths is influenced by patients' effort. The inspiratory phase of the respiratory cycle is typically patient-triggered, but can also be mechanically triggered when the ventilator switches into apnea mode. The most common assisted ventilation modes used in the intensive care unit (ICU) are assist-control ventilation (ACV), and pressure-support ventilation (PSV) (7-10,17,18). The main difference between these ventilation modes is the controlled variable, ACV controls VT and PSV controls Pinsp. In PSV, the level of Pinsp is called pressure support (PS). The relationship between VT and PS depends on the mechanical characteristics of the respiratory system (i.e. resistance and compliance) and patients' muscle generated pressure

(Pmus) (9,14,19,20). During ACV or PSV, patients determine their fR, and in PSV patients determine their VT and fR.

ACV is a volume-controlled, time cycled, patient-triggered, ventilation mode (10,15), meaning that the ventilator supplies a determined VT within a fixed time, when patients generate spontaneous breathing effort. The settings for ACV are: inspiratory tidal volume (VT) that the ventilator delivers for each breath; inspired fraction of oxygen (FIO_2); inspiratory time (Ti), which is the time required to achieve VT according to the set inspiratory flow; inspiratory flow ($\dot{V}i$), which usually is constant, and depends on the inspiratory flow pattern; inspiratory flow pattern, which defines the shape of the flow profile provided to the patient, which can be either constant, accelerating, or decelerating; trigger sensitivity, which is the patient generated inspiratory flow (or pressure) required to trigger the delivery of inspiratory flow; back-up respiratory frequency or apnea setting, is the minimum respiratory frequency of the patient, below this value, the ventilator starts delivering mechanically triggered breaths; and level of positive end expiratory pressure (PEEP).

PSV is a pressure-controlled, flow cycled, patient triggered, ventilation mode (9,15,21), meaning that the ventilator supplies a determined PS during a time interval that is actively determined by the patient with via an inspiratory flow-based criterion, when patients generate a spontaneous breathing effort. The settings for PSV are: level of inspiratory pressure or pressure support (PS) that the ventilator delivers for each breath during the inspiration; inspired fraction of oxygen (FIO_2); ramp time or slope, which is the time the ventilator takes to reach the PS level; cycling to expiration criterion, which defines the decrease in inspiratory flow needed to actively terminate the inspiratory phase of the respiratory cycle; trigger sensitivity, which is the patient generated inspiratory flow (or pressure) required to trigger the delivery of inspiratory flow; back-up respiratory frequency or apnea setting, is the minimum respiratory frequency of the patient, below this value, the ventilator starts delivering mechanically triggered breaths; and level of positive end expiratory pressure (PEEP).

1.3. CHALLENGES OF MECHANICAL VENTILATION

The process of finding and selecting ventilator settings to optimize the work of breathing promote removal of CO_2 and delivery of O_2 without inducing lung damage, is difficult. Patients may require very different ventilator settings, according to their underlying physiological abnormalities and may respond quite differently to changes in ventilator support. The challenges of mechanical ventilation when using to the two major ventilation modes are summarized in the following sub-sections.

1.3.1. CHALLENGES OF CONTROLLED VENTILATION

Physicians confront several conflicting therapeutic goals when selecting ventilator settings for patients in controlled ventilation modes. Patients may require large $\dot{V}E$, high PEEP levels and high FIO_2 to maintain normal acid-base and oxygenation status. Large $\dot{V}E$ is, however, often obtained using high values of Pinsp, VT and fR, all of which can promote ventilator induced lung injury (VILI) (22). Indeed, low $\dot{V}E$ and the subsequent permissive hypercapnia is usually accepted in patients with severe respiratory abnormalities to avoid VILI (23,24). The most common VILIs are barotrauma/volutrauma caused by lung over-distention due to high Pinsp or VT, and atelectrauma caused by repeated opening and closing of collapsed alveolar units (atelectasis) (22,25). Avoiding barotrauma/volutrauma can be achieved by limiting Pinsp or/and VT settings on the ventilator. In contrast, to avoid atelectrauma, it may be necessary to reopen collapsed alveolar units with a recruitment maneuver (25). When successful, recruitment is usually followed with an increase of PEEP to counteract the compressive forces acting on the recently reopened (or recruited) alveolar units, and by reducing FIO_2 to prevent the collapse of low ventilation-perfusion ratio ($\dot{V}/\dot{Q}$) alveolar units due to gas-absorption atelectasis (22,26,27). Thus, selecting the appropriate $\dot{V}E$ to promote removal of CO_2 and delivery of O_2, keeping adequate blood acid-base and oxygenation status, requires that physicians balance the risk of developing hypercapnia against the risk of developing VILI. In a similar way, selecting the appropriate level of PEEP to keep the lung open, requires that physicians balance the risk of increasing the stress and strain of already open lung regions, against the risk of alveolar collapse when decreasing PEEP (22). Selecting the appropriate FIO_2 to achieve adequate oxygenation, requires that physicians balance the risk of hypoxemia when decreasing FIO_2, against the risks of developing absorption atelectasis (28) or oxygen induced lung edema and cellular death (29), on increasing FIO_2.

1.3.2. CHALLENGES OF ASSISTED VENTILATION

Similar conflicting therapeutic goals exist in assisted ventilation modes i.e. selecting VT or PS levels, to promote removal of CO_2 and delivery of O_2, keeping adequate blood acid-base and oxygenation status without increasing the risk of developing VILI; and selecting PEEP and FIO_2 to ensure adequate oxygenation without increasing the risk of developing gas-absorption atelectasis, and oxygen induced lung edema and cellular death. In addition, during assisted ventilation, physicians often search for an optimal setting of volume or pressure by titrating the level of ventilator support (VT or PS), and evaluating patients' response. The individual patient clinical response is

typically evaluated with measurement of arterial blood gases (ABG), pulse oximetry, capnography, changes in fR and VT, or assessing for increased work of breathing by observation or palpation of accessory respiratory muscles (e.g. sternocleidomastoid) (9,10).

After modifying the level of ventilator support, physicians also often take into account the effects of excessive or too little support (9,17,21,30). Excessive support may increase the number of ineffective triggering efforts and induce respiratory muscle atrophy with the patient effectively being ventilated as in controlled ventilation mode. Too little support may cause respiratory distress, reduce alveolar ventilation ($\dot{V}A$) and compromise blood acid-base status, increase patients' work of breathing, and induce respiratory muscle fatigue (31). On reduction of the level of ventilator support, if patients show inadequate response (e.g. respiratory distress, significant increase of work of breathing, anxiety, reduction SaO_2 and PaO_2, or increase of $PaCO_2$ and $FECO_2$), physicians typically increase the level of support in order to improve ventilation, and reduce the work of breathing.

This section has highlighted the challenges facing clinicians when deciding upon appropriate ventilator therapy. Several clinical and technological solutions have been proposed for aiding clinicians in selecting appropriate settings. The following section reviews the state of the art of such solutions.

1.4. CURRENT CLINICAL AND TECHNOLOGICAL SOLUTIONS FOR IMPROVING MECHANICAL VENTILATION

Current solutions for selecting adequate ventilator settings can be divided in two categories: clinical and technological. Clinical solutions include clinical recommendations, like the ARDSnetwork guidelines (32), which have been developed as the result of clinical studies designed to develop strategies for lung-protective and safe ventilation (23,24). Technological solutions include decision support systems (DSSs), which are computer systems either controlling or providing advice on appropriate ventilator settings. These systems are either rule-based systems, model-based systems or hybrid systems (which combine rule and model-based systems). DSSs can aid in setting the ventilator in two different ways. Rule-based systems mimic physicians' clinical decisions by applying artificial-intelligence algorithms. Model-based and hybrid systems simulate patients' response via physiological models, and then generate advice on ventilator settings, according to simulated patient responses. The following text presents a summary of clinical and technological solutions applied to help in selecting ventilator settings in the two major ventilator modes.

1.4.1. CURRENT SOLUTIONS FOR IMPROVING THE SELECTION OF VENTILATOR SETTINGS IN CONTROLLED VENTILATION

1.4.1.1 Use of clinical solutions for improving controlled ventilation settings

Several clinical recommendations have been developed and evaluated for providing lung-protective and safe ventilation in patients with acute respiratory distress syndrome (ARDS) (23,24). Application of these recommendations have, primarily through the provision of low VT, been shown to reduce both mortality and weaning time (32). Current clinical guidelines recommend the ventilator be set to a VT of 6 ml/kg of predicted body weight (PBW), plateau pressure <30 cm H_2O, and FIO_2 required to achieve 88 %<SaO_2<95 %. These guidelines are considered as the “gold standard” for ventilating safely ALI/ARDS patients in controlled ventilation modes (32).

1.4.1.2 Use of technological solutions for improving controlled ventilation settings

In controlled ventilation modes, DSSs have been developed which combine mathematical models of several physiological systems, with these used to describe and simulate patients’ response to changes in ventilator settings (6,33-36). One such system is the INVENT system (1,6). This is a model-based DSS that includes models of: blood acid-base status (37,38); body buffering (O_2 and CO_2 transport and storage) (39); and pulmonary gas-exchange (40), plus rudimentary models of lung mechanics and circulation. INVENT has been evaluated retrospectively and prospectively to describe patients in controlled ventilation, with a wide range of abnormalities of pulmonary gas-exchange and blood acid-base status (2-5). INVENT’s retrospectively generated advice on controlled mode settings has been shown to be in agreement with ARDSNetwork guidelines for providing safe ventilation (2-5).

1.4.2. CURRENT SOLUTIONS FOR IMPROVING THE SELECTION OF VENTILATOR SETTINGS IN ASSISTED VENTILATION

1.4.2.1 Use of clinical solutions for improving assisted ventilation settings

As for controlled ventilation, recommendations for ventilating patients in assisted ventilation must provide protective ventilation, and reduce the risk of developing VILI. In addition, selecting the appropriate level of ventilator support requires consideration of patient synchrony with the ventilator, and

risk of development of respiratory muscles fatigue or atrophy. The current clinical recommendation is to set the level of PS to the individual patient, in order to achieve a VT of 6 ml/kg of PBW. Reduction of PS has been associated with increase of synchrony between patient and ventilator. Reducing PS from 20 to 13 cm H_2O resulted in a significant reduction of number of ineffective triggering events, and a VT of 6 ml /kg of PBW (41,42). Interestingly, setting the level of PS in order to achieve a low VT (6 ml/kg of PBW), provided better gas-exchange (measured as FRC) than using a level of PS in order to achieve high VT (8 ml/kg of PBW) (18).

1.4.2.2 Use of technological solutions for improving assisted ventilation settings

DSS have been incorporated into two commercially available ventilation modes, with these ventilator modes being capable of automatically modifying the level of ventilator support (43). These systems are SmartCare/PS and Adaptative Support Ventilation (ASV). As illustrated in figure 1-1 both of these systems measure patients response to changes in ventilator settings and automatically use this response as feedback to adapt the level of ventilator support.

SmartCare P/S is rule-based DSS, which integrates an artificial intelligence algorithm that mimics physicians' actions in changing the level of pressure support (PS) (16,44). The ventilator operating under SmartCare P/S, provides PS so as to maintain the patient's breathing pattern within a comfort zone of ventilation, which is delimited by 12/min < fR <30/min and $FECO_2$< 0.077 (55 mm Hg) (45). If patients are stable within the comfort zone, the ventilator automatically starts a progressive reduction of PS, and evaluates whether or not the patient is ready for extubation (46). To evaluate patients' response, this ventilator mode requires continuous monitoring of fR, VT and $FECO_2$.

ASV is hybrid DSS, which integrates a physiological model of work of breathing and a rule-based algorithm to provide safe limits of VT and fR, and to reduce the risk of developing intrinsic PEEP (16,44,47). The ventilator operating under ASV, provides sufficient PS to maintain the patient's ventilation with the optimal VT and fR combination required to reduce the rate of work of breathing according to a physiological model (48). The ventilator modifies the level of PS required to meet the targeted VT and fR combination in response to patient effort and changes of the time constant of the respiratory system, the latter being estimated form the expiratory flow (49). A new implementation of this ventilator mode is IntelliventASV, which is designed to maintain a level of $FECO_2$ determined by the physician, adjust PEEP-FIO_2 according to the ARDSnetwork tables to maintain acceptable levels of SpO_2, in addition to the optimal VT and fR combination (50-53).

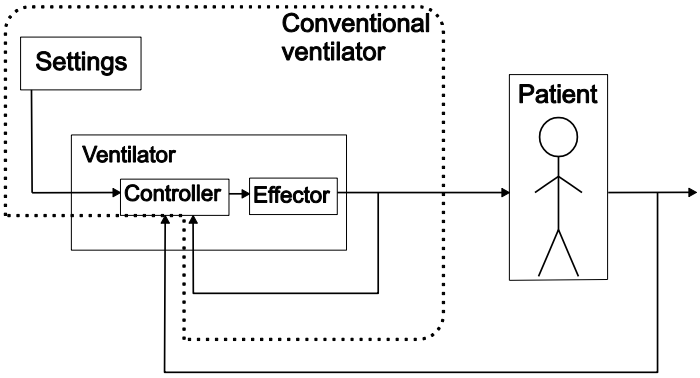

Figure 1-1. Representation of DSS integrated into ventilator modes. The ventilator is composed of two components. The effector is the hardware that allows the delivery of inspiratory gas and waste of expiratory gas. The controller is composed of software and microprocessors that control the effector. The controller of ventilators including the ventilation modes SmartCare P/S and ASV, receives input signals from the patient. These signals can be $FECO_2$, fR or/and SpO_2, and are used among ventilator settings to determine the level of PS provided to the patient. The control circuit of conventional ventilator is indicated inside the dotted area.

Other ventilator modes have been developed for delivering a breath-by-breath customized level of ventilator support, according to an amplified signal of continuously measured patient-effort. This signal is also employed to trigger delivery of inspiratory flow, and to determine the level of ventilator support provided for each breath. Proportional-assisted ventilation (PAV) is a ventilator mode that uses the instantaneous inspiratory flow to increase the airway pressure in proportion to patient effort (16,44,54). PAV has been shown to reduce dyssynchrony between patient and ventilator (55). Neurally adjusted ventilation (NAVA) is a ventilator mode that uses the electrical activity of the diaphragm (EAdi) to trigger, increase, and modulate, the airway pressure (16,44). NAVA has been shown to increase patient synchrony with the ventilator (56).

The above mentioned DSSs and ventilator modes determine the level of PS based upon either rules, work of breathing, mechanical characteristics of the respiratory system or surrogate signals of patients' effort. These systems and ventilation modes do not provide a complete description of patients' physiology, including, for example, the relationship between ventilation and acid-base status.

This section has addressed the clinical challenges of mechanical ventilation and clinical and technological solutions. Clinical studies have shown that mechanical ventilation needs to be administered with protective settings, in order to reduce the risk of inducing VILI. Clinical solutions such as guidelines and recommendations have been established to protect patients from deleterious effects of mechanical ventilation and aid physicians to select adequate ventilator settings. In addition, technological solutions have been developed to aid physicians. Model-based DSS can describe and simulate patients' response to changes in controlled ventilation, and hence, can provide advice in accordance to the protective guidelines for mechanical ventilation. Alternatively, rule-based and hybrid DSSs, already included in ventilator modes, can modify the level of PS according to patients' response within, limits programed within the systems' algorithms or set by the physician. The next section describes the limitations of the current clinical and technological solutions used to set mechanical ventilation.

1.5. LIMITATIONS OF THE CURRENT CLINICAL AND TECHNOLOGICAL SOLUTIONS FOR IMPROVING MECHANICAL VENTILATION SETTINGS

Despite having shown clinical benefit, current clinical and technological solutions for improving mechanical ventilation can be seen as having limitations. Clinical guidelines are general recommendations for ventilating patients, with limited patient specific advice or interpretation of the underlying physiological state of the individual patient. Technological solutions include those that are model-based, rule-based or hybrid systems, but these approaches can currently be seen as having a number of important limitations. This section describes the limitations of current solutions, highlighting the need for further work.

1.5.1. LIMITATIONS OF CLINICAL SOLUTIONS

The use of general recommendations for providing lung-protective ventilation to patients in controlled-ventilation with heterogeneous lung abnormalities may be misleading. Several studies (57,58) have pointed out that the guidelines for providing protective ventilation to patients with ALI/ARDS may not be applicable for all ventilated patients. For instance, critically ill patients with severe pulmonary abnormalities (e.g. low FRC and low compliance) may be at risk of developing VILI when ventilated with 6 ml/kg PBW. Conversely, patients without pulmonary abnormalities may be suitable for being ventilated with VT higher than 6 ml/kg PBW (58). It may therefore be argued that the

selection of ventilator settings needs to be performed accounting for individual patients' physiological conditions (25,57-59).

The general recommendation for setting adequate level of PS i.e. setting PS to achieve a VT of 6 ml/kg of PBW, to spontaneously breathing patients, highlights the importance of providing individualized ventilation and understanding patients' physiology. PS is adjusted to produce a low level of VT considering: individual patients' PBW; patient respiratory effort; and characteristics of the respiratory system (17,20,30). In addition, low VT requires adequate levels of PEEP and FIO_2, to maintain stable alveolar units (22,26,60), and encourages reduction of PS, which is associated with a reduction the number of missing efforts due to over-support (42).

1.5.2. LIMITATIONS OF TECHNOLOGICAL SOLUTIONS

The use of physiological models to simulate individual patients can be used to provide appropriate ventilator settings tailored to individual patients' physiological conditions. INVENT is a DSS that includes physiological models of pulmonary gas-exchange, blood acid-base status, and body buffering. The set of physiological models included in INVENT has however been limited to describe patients in controlled ventilation, as the set of models does not include a mechanism that controls ventilation to regulate arterial pH (pHa), or arterial partial pressure of CO_2 ($PaCO_2$) i.e. model of respiratory control. Hence, INVENT has not been developed to provide advice for describing spontaneously breathing patients in support ventilation (6).

The integration of rule-based and hybrid DSS into ventilator modes, has enabled ventilators to have the capability of automatically modifying the level of PS in response to changes in patients' breathing pattern. SmartCare P/S adapts the level of PS in order to maintain patients' breathing pattern (VT, fR, and $FECO_2$) in a comfort zone. ASV adapts the level of PS according to changes in compliance and resistance, in order to maintain optimal VT and fR. Both systems, modify PS to produce a respiratory pattern, which is acceptable according to each system's limits, rather than describing (and understanding) individual patients. Describing patients' response is difficult because the effects of modifying for example PS, may affect different physiological processes involved in ventilation, e.g. pulmonary gas-exchange, blood acid-base status and respiratory control (17,20,30). The use of physiological models to describe those physiological processes may be a useful way to combine their effects, and hence, describe patients' respiratory response. Patients' response to changes in mechanical ventilation settings during controlled ventilation has been described using the set of models included in the INVENT system. This system includes physiological models which can be tuned to describe individual patients' physiological

abnormalities. The use of such physiological models for describing patients' response during controlled ventilation, might be extended to describe spontaneously breathing patients in support ventilation. To do so requires integration of a model of respiratory control to existing models included in the INVENT system (6).

1.6. AIMS OF THE PHD THESIS

This chapter has described the typical modes of mechanical ventilation and the challenges and current solutions to those challenges. It can be concluded that there does not currently exist a technological solution to the challenge of setting support ventilation which adequately describes individual patients' physiology and therefore enables simulation of response to changes in ventilator support. Several model components to such technological solution exist within the INVENT system, but this lacks integration of a model of respiratory control if it is to provide advice in assist modes of ventilation. The aim of this PhD thesis is therefore to investigate whether it is possible to identify a suitable model of respiratory control and integrate this into existing INVENT models. The resulting model, including that for respiratory control, should be useful at the bedside, meaning that it must be possible to tune the model to the individual patient's conditions only with clinically available data. When tuned, it should be possible to describe patients' state, predict patients' response to changes in the level of ventilator support, and evaluate whether the integrated models enable description of patients in assisted ventilation. It is therefore also an aim of this thesis to evaluate the integrated models with prospective clinical studies. The strategy for each of these tasks is outlined below with the details given in subsequent chapters of the thesis.

- Review and selection of models

Chapter 2 describes the selection process of an appropriate respiratory control model to be integrated into the set of physiological models of INVENT. So far, it has been assumed that the set of models included in INVENT are appropriate to describe patients' response. Whether this assumption is valid in the context of other physiological models described in the literature is reviewed in section 2.1. To do so, a brief description of the models included in INVENT is presented in section 2.1.1. The criteria for reviewing physiological models similar to INVENT's set of models is presented in section 2.1.2. The review of physiological models is presented in section 2.1.3. A summary of the review of physiological models describing the relationship between blood acid-base status and ventilation is presented in section 2.1.4. The additional model components required to describe how ventilation is generated (a mechanism that controls ventilation to regulate either arterial hydrogen ion concentration in the arterial blood ($[H^+a]$), pHa or

$PaCO_2$) and hence, allow description spontaneously breathing patients, are described in section 2.1.5.

Published physiological models of respiratory control are reviewed in section 2.2. A brief description of respiratory control physiology is presented in section 2.2.1. The criteria for reviewing respiratory control models is presented in section 2.2.2. The review of the respiratory control models is presented in section 2.2.3, and the selection of the respiratory control model that best met these criteria is presented in section 2.2.4.

- Integration of models

Chapter 3 presents the integration of the selected respiratory control model into INVENT's set of models. As will be shown in this chapter, the selected respiratory control model required several modifications, these being necessary to allow description of patients on assisted ventilation modes (section 3.2). Two additional models, were required to complete the description of patients in assisted ventilation modes. These were a model of muscle function, described in section 3.3, and a model of effective compliance, described in section 3.4.

- Evaluation of the integrated model

Chapter 4 describes the verification of the INVENT's set of models including the respiratory control model. The models were verified against literature data, to see if they could adequately describe typical effects of abnormal blood acid-base status on ventilation (section 4.2.1). In addition, chapter 4 presents a sensitivity analysis of the model parameters included in the respiratory control model illustrating which patient-specific model parameters could be identified from clinical data (section 4.2.2). Section 4.3 describes the parameter estimation method used for estimating patient-specific model parameters and, as such, tuning the respiratory control model to specific patients.

Chapters 5 and 6 describe the clinical evaluation of the INVENT's set of models including the respiratory control model. Model simulated values of patient response were compared against data collected from two prospective clinical studies, performed as part of this PhD thesis. In these studies, patients were subjected to up to 5 different levels of ventilator support. The two studies were performed with different assisted ventilation modes i.e. assisted controlled-volume support ventilation (ACV) and pressure support ventilation (PSV), respectively.

CHAPTER 2. REVIEW AND SELECTION OF MODELS

The previous chapter outlined the potential for using physiological models to describe patients' response to changes in the level of ventilator support. In this chapter, published physiological models describing the relationship between blood acid-base status and ventilation, and physiological models of respiratory control are reviewed, and a physiological model of respiratory control is selected to be included in to the set of models of INVENT. Section 2.1 presents the review of physiological models describing the relationship between blood acid-base and ventilation. Section 2.2 presents the review of respiratory control models, and the selection of the model of respiratory control that will be included into INVENT's set of models.

2.1. REVIEW OF PHYSIOLOGICAL MODELS DESCRIBING THE RELATIONSHIP BETWEEN BLOOD ACID-BASE STATUS AND VENTILATION

Physiological models describing the relationship between blood acid-base status and ventilation that are similar to the set of models of INVENT are reviewed, in order to validate the assumption that the INVENT's set of models is appropriate to describe patients' response.

2.1.1. DESCRIPTION OF INVENT'S SET OF MODELS

Figure 2-1 illustrates the set of physiological models included in INVENT. The set of models includes lung mechanics, pulmonary gas-exchange, blood acid-base status, and body buffering. INVENT is a DSS, which applies this set of physiological models to describe patients current state, and then, generates advice for selecting settings of controlled ventilation modes (i.e. FIO_2, VT, and fR). The advice is generated as follows: First, model parameters describing pulmonary gas-exchange and blood acid-base status are tuned to patient-specific conditions through an experimental procedure, which involves 3-5 step changes in FIO_2 (61,62). Then, the values of model parameters are considered as constants. Second, the set of physiological models, and patient-specific model parameters are used to perform a series of simulations with different ventilator settings. Third, the detrimental effects of simulated patient-specific responses (with outcomes e.g. PaO_2, $PaCO_2$, pHa) are quantified with penalty functions, which reflect clinical preferences to patient's outcome and ventilator settings, in a decision theoretic approach. INVENT's advice is then the simulated patient response that best balances simulated

ventilator settings, which is found with a mathematical optimization process that minimizes the associated penalty (1,6). The physician in charge of setting the ventilator is then in position of accepting or rejecting INVENT's advice, i.e. an open-loop decision support system (figure 2-1). The importance of using physiological models relies on the necessity of adequately describing patients' response to changes in mechanical ventilation, in order to adequately simulate patients' outcomes, and hence provide advice.

Different physiological models describing the relationship between blood acid-base status and ventilation have been developed and published. The next sub-section describes criteria for reviewing such physiological models in comparison to INVENT's set of models, the aim being to evaluate the appropriateness of the models included in the INVENT system.

2.1.2. CRITERIA FOR REVIEWING PHYSIOLOGICAL MODELS SIMILAR TO INVENT'S SET OF MODELS

As highlighted in the previous sub-section, physiological models are essential for describing patients' response to changes in mechanical ventilation. The models must describe patients with different physiological abnormalities through tunable model parameters. Previously, a set of models has been formulated for use in the INVENT system describing the relationship between blood acid-base status and ventilation. This section reviews other similar published models, using a set of criteria, to see if they have functionality similar to the requirements of the current INVENT system. The following criteria are used in this process:

1. Model parameters can be tuned with clinically available data.
2. Model parameters are identified with a well-established and described method. The model parameters may not be tuned with non-standard or special measurements that are not available in the ICU.
3. Model parameters have a physiological interpretation, and as such may provide deeper understanding of patients' physiology.
4. Model complexity includes description of pulmonary gas-exchange.
5. Model complexity includes description of blood acid-base status.
6. Model complexity includes description of body buffering.
7. Models have been adequately evaluated and shown to describe the effects of abnormal pulmonary gas-exchange and blood acid-base status.

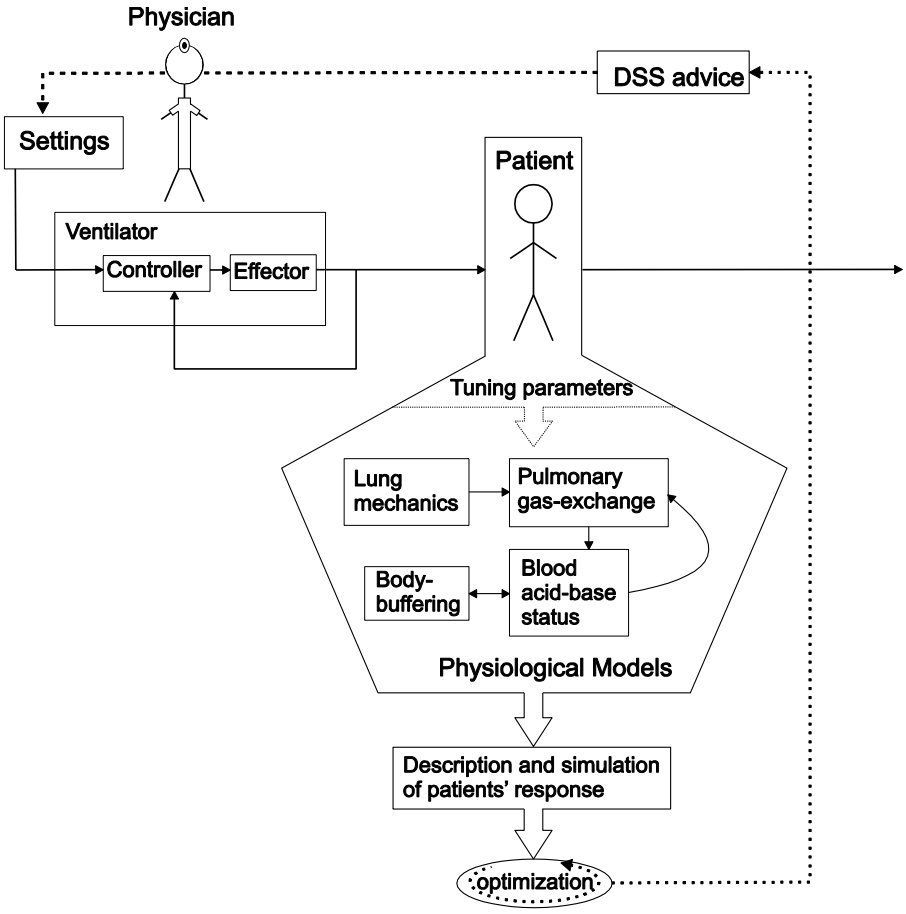

Figure 2-1. Structure of the INVENT DSS. The system components are: a set of physiological models (represented with the connected and interconnected boxes inside the pentagon); a method to identify model parameters (represented with the arrow below the patient); and an optimization process according to penalty functions (represented with the oval). Patients' response is described and simulated with a set of physiological models (with outcomes e.g. PaO_2, $PaCO_2$, pHa). The set of models includes lung mechanics, pulmonary gas-exchange, blood acid-base status, and body buffering. To describe individual patients' response, the parameters of the set of models are tuned to the individual patient and used to simulate patient response to changes in ventilator settings (represented with the box below the pentagon). Through a series of simulations, the DSS can optimize ventilator settings according to penalty functions, which quantify the clinical preference to patients' outcomes and side-effects of ventilator settings. The "optimal" ventilator settings are those resulting in the minimal penalty (represented as DSS advice). The physician is then in position of accepting or rejecting the DSS advice, and modify the ventilator settings.

2.1.3. REVIEW OF PHYSIOLOGICAL MODELS SIMILAR TO INVENT'S SET OF MODELS

Table 2-1 summarizes this review of 16 published physiological models of pulmonary gas-exchange and blood acid-base status. All models were reviewed according to the criteria presented in 2.1.2, with the first two columns of table 2-1 listing the main author and name of the models, respectively, and the rest of the columns representing a single criterion. Table cells contain either 'yes' or 'no', denoting whether each model meets the requirement. The third column, also includes the legend 'sim', which is used to denote complex models that cannot be identified with clinical data. The ninth column indicates whether each model includes additional model complexity.

The model of West (63) was developed to simulate the effects of ventilation and perfusion ($\dot{V}/\dot{Q}$) impairment at different conditions of FIO_2, $\dot{V}E$, and blood characteristics (base excess or hemoglobin concentration). A method for determining patient-specific model parameters was developed latter (64) which employed a mixture of (six) inert gases that is infused to the test subject with gas concentrations measured in exhaled gas and arterial and mixed venous blood. The retention and excretion of these gasses were calculated from measured concentrations for each infused gas, and these values used to determine model parameters. This procedure, known as the Multiple Inert Gas Elimination Technique (MIGET) is considered the reference technique for measuring ventilation-perfusion distribution ($\dot{V}/\dot{Q}$) in the lungs. Model parameters have physiological interpretation, indeed much of that which is known about gas exchange impairment in the lungs has been learned from application of MIGET (28,65). The use of multiple gasses, not available in a standard clinical setting, and complex measurement technology usually limits its application outside the experimental setting. The model describes different physiological conditions, and allows the simulation of the effects of changes in ventilation on arterial and mixed-venous partial pressures of O_2 and CO_2. The model has been evaluated in healthy subjects (64) and patients with COPD (66-69), ARDS (70,71), and prone position in ARDS (72,73).

The model of Dickinson, is included in a simulation program (MacPuf) that can be used to describe spontaneously breathing patients on mechanical ventilation. This model could not be used due to restrictions on computer power when it was developed. Recently, Jouvet (74) applied this model into a new simulation program (SimulResp) that describes the effects of changes in mechanical ventilation in pediatric patients. There is no description of a method for determining patient-specific parameter values. SimulResp's parameters have physiological interpretation e.g. functional residual capacity (FRC), compliance (C), and resistance (R). SimulResp includes a description

of pulmonary gas-exchange, blood acid-base, body buffering, respiratory drive, cerebral blood flow, and lung mechanics. SimulResp has been used for simulation of different physiological conditions, however no clinical evaluations for describing individual patients have been performed (75).

The model of Rutledge (76) is included in a simulation program (VentSim) that describes the effects of changes in mechanical ventilation on PaO_2 and $PaCO_2$. Model parameters were input by the user of the program, and there is no description of a method for determining patient-specific parameter values. VentSim's parameters have physiological interpretation e.g. shunt fraction (fs), fraction of perfused pulmonary compartments (fp1 and fp2), and volume of ventilated pulmonary compartments (VA1 and VA2). VentSim includes a description of pulmonary gas-exchange, but lacks description of blood acid-base status and body buffering. VentSim has been used for simulating the effects of changes in mechanical ventilation, however, no clinical evaluations for describing individual patients have been performed.

The model of Winkler (77) is included in a simulation program (SimuVent) that describes the effects of changes in mechanical ventilation on lung mechanics, and gas exchange, transport and mixing. There is no description of a method for determining patient-specific parameter values, so that, the user of the program inputs the values of model parameters. SimuVent's parameters have physiological interpretation, e.g. resistance (R), compliance (C), functional residual capacity (FRC). SimuVent includes a description of pulmonary gas-exchange, blood acid-base status and oxygenation, and lung mechanics, but lacks from a description of the effects of body buffering. SimuVent has been used for simulating the effects of mechanical ventilation, however no clinical evaluations for describing individual patients have been performed.

The model of Vidal-Melo (78) (2C) was developed to describe and quantify the effects of ventilation and perfusion ($\dot{V}/\dot{Q}$) impairment with a 2 lung-compartment (2C) model. A method for determining patient-specific model parameters is described. This method includes an experimental procedure where the level of FIO_2 is modified in two different occasions until reaching steady state. Arterial blood gases (ABG), oxygen consumption ($\dot{V}O_2$) and production of ($\dot{V}CO_2$) are measured at each level of FIO_2.These measurements are then used to determine the values of model parameters. The model parameters have physiological interpretation, and parameter values can be used for describing pathological conditions e.g. the logarithmic mean and standard deviation of the $\dot{V}/\dot{Q}$ distribution. The 2C model includes description of pulmonary gas-exchange, blood acid-base status and oxygenation, and buffer capacity buffering (BC). The 2C model has been eva-

Table 2-1 Review of physiological models describing the relationship between blood acid-base status and ventilation.

		Model parameters			**Model complexity**
Autors	Name of the system or model	Tunable to individual patient with clinical data	Well-established and described tuning method	Physiological interpretation	Pulmonary gas-exchange
West, Wagner (63,64)	MIGET	sim no	yes	yes	yes
Dickinson, Jouvet (74)	MacPuf SimulResp	no	no	no	yes
Rutledge (76)	VentSim	sim	no	yes	yes
Winkler (77)	SimuVent	sim	no	yes	yes
Vidal-Melo (78)	2C	yes	yes	yes	yes
Hardman (36,79)	NPS	yes	yes	yes	yes
Kwok, Wang (33,80)	SIVA-SOPAVent	yes	yes	no	yes
Rees (1)	INVENT	yes	yes	yes	yes
Ben-Tal (81)	ns	sim	no	yes	yes

Table 2-2 Review of physiological models describing the relationship between blood acid-base status and ventilation (continuation).

	Model complexity			
Autors	Blood acid-base and oxygen-nation	Body buffering	Others	Clinical evaluation of the model
West, Wagner (63,64)	yes	no	---	yes
Dickinson Jouvet (74)	yes	yes	respiratory drive, lung mechanics	no
Rutledge (76)	no	no	lung mechanics	no
Winkler (77)	yes	no	lung mechanics, circulatory system	no
Vidal-Melo (78)	yes	yes	---	yes
Hardman (36,79)	yes	yes	lung mechanics, circulatory system	no
Kwok, Wang (33,80)	yes	no	lung mechanics	yes
Rees (1)	yes	yes	lung mechanics	yes
Ben-Tal (81)	yes	no	respiratory control	no

Table 2-3 Review of physiological models describing the relationship between blood acid-base status and ventilation.

		Model parameters			**Model complexity**
Autors	Name of the system or model	Tunable to individual patient with clinical data	Well-established and described tuning method	Physiological interpretation	Pulmonary gas-exchange
Chakrabotty (82)	Multiscale pulmonary model	sim	no	yes	yes
Kapitan (83)	ns	sim	no	yes	yes
Chbat Albanesse (84,85)	CP	sim	no	no	no
Wilson (86)	ns	yes	yes	yes	yes
Reynolds (87)	ns	sim	no	yes	yes
Kretschmer (88)	Beat-to-beat	yes	yes	yes	yes
Schadler (89)	EWS	yes	yes	---	yes

luated in healthy subjects and COPD patients at different conditions e.g. high altitude. Evaluations have been performed in animal models on mechanical ventilation (90).

The Nottingham Physiological Simulator (NPS) (79,91) is a simulation program that describes physiological processes, including pulmonary gas exchange, blood acid-base status, circulation, and metabolism. Recently, a method for tuning this system to describe ventilated patients has been implemented and evaluated in COPD patients (36). NPS has been used to optimize mechanical ventilation settings to avoid VILI and simulate recruitment maneuvers (92,93). NPS includes description of pulmonary gas-

Table 2-4 Review of physiological models describing the relationship between blood acid-base status and ventilation (continuation).

	Model complexity			
Autors	Blood acid-base and oxygen-nation	Body buffering	Others	Clinical evaluation of the model
Chakrabotty (82)	yes	no	capillary dilatation, red cell morphology	yes
Kapitan (83)	yes	no	---	no
Chbat Albanesse (84,85)	yes	no	lung mechanics, circulatory system, respiratory control	no
Wilson (86)	yes	no	lung mechanics, tracheal tree CFD, pulmonary circulation	yes*
Reynolds (87)	yes	no	inflammation model	no
Kretschmer (88)	yes	no	---	yes
Schadler (89)	yes	no	lung mechanics	yes

exchange, blood acid-base and oxygenation, and body buffering, in addition to lung mechanics and circulatory system. NPS has been used for simulate different physiological conditions. Evaluations describing vitual patients with ARDS and COPD have been performed (93-96).

The Sheffield Intelligent Ventilator Advisor (SIVA) (33,97) is a hybrid DSS that employs the physiological model ‘Simulation of patients under artificial ventilation’ (SOPAVent) to describe the effects of changes in mechanical ventilation on blood acid-base status. SOPAVent uses a fuzzy logic algorithm with includes models of $\dot{V}CO_2$ and pulmonary shunt, which are necessary for

determining the value of the patient-specific parameter 'relative dead space' (Kd) (80). The model parameter Kd, depends on fuzzy-logic rules. SIVA-SOPAVent includes a description of pulmonary gas-exchange, blood acid-base status and oxygenation, and lung mechanics, but does not include a model of body buffering. SOPAVent has been evaluated in patients on mechanical ventilation, and was shown to provide acceptable model predictions of $PaCO_2$, PaO_2, and pHa (80).

The Intelligent Ventilator (INVENT) (1) is a model-based DSS, which generates advice for setting mechanical ventilation. The advice is found by optimizing patient-specific simulations considering penalty functions that reflect clinical preferences over ventilator settings and the simulated patients' outcome (98). A method for determining patient-specific model parameters is described. This method includes an experimental procedure, where FIO_2 is modified in 3 to 5 step changes until the patient reaches steady state (61,62). Continuous measurements of pulse oximetry saturation, FIO_2, $FECO_2$, FEO_2, inspiratory and expiratory flow, and a single arterial blood gas (ABG) measurement taken at the beginning of the experiment are required for determining the value of model parameters. Most measurements are available in the clinical setting but it does require both volumetric capnography and indirect calorimetry. INVENT's parameters have physiological interpretation, model parameters describing pulmonary gas-exchange are: shunt fraction (fs); fraction of ventilation to alveolar compartment 2 (fA2); and fraction of perfusion to compartment 2 (f2) (40). INVENT includes a description of pulmonary gas-exchange, blood acid-base status and oxygenation, body buffering, and lung mechanics. INVENT has been evaluated retrospectively and prospectively to describe patients status during controlled ventilation, and to generate advice for FIO_2, VT and fR (2,4,5).

The model of Ben-Tal (81) was developed to describe the respiratory control, as such, the model includes a mono-compartmental description of pulmonary gas-exchange and blood acid-base status. There is no description of a method for determining patient-specific parameters, because the aim of the model of pulmonary gas-exchange is not to describe ventilation-perfusion impairment. Ben-Tal's model includes a description of pulmonary gas-exchange, blood acid-base status, and respiratory control, but lacks description of body buffering. This model has not been evaluated for describing patients on mechanical ventilation.

The model of Chakrabotty (82) is a multi-scale physiological model, which has been developed for describing the lungs function from a micro, meso and macro scale. There is no description of a method for determining patient-specific parameters. The model has a large number of model parameters and

provides an insight to pathologies that increase high $\dot{V}/\dot{Q}$ regions of the lung. The model includes a description of pulmonary gas-exchange, blood acid-base status and oxygenation, pulmonary capillary circulation, and red-blood cell oxygen saturation, but does not include a model of body buffering. This model has been evaluated qualitatively to describe hepatopulmonary syndrome.

The model of Kapitan (83) is included in a patient simulator program, which is used for training physicians, and simulating different conditions of pulmonary gas-exchange, blood acid-base abnormalities, circulation and metabolism. Although Kapitan's model has the potential for describing patients' response, there is no description of a method for determining patient-specific parameter values. This model is capable of simulating different physiological conditions, but no clinical evaluations for describing individual patients have been performed.

The cardio pulmonary (CP) model (84,85) is a physiological model capable of simulating changes in pulmonary gas-exchange, circulation and respiratory control for a variety of physiological conditions. There is no method for determining the values of patient-specific model parameters, which are input by the user. CP's pulmonary gas-exchange parameters have physiological interpretation e.g. pulmonary shunt (Fsh), blood flow to the pulmonary capillary (Fpp). This model includes a description of pulmonary gas-exchange, blood acid-base, cardiovascular system, lung mechanics, and respiratory control, but not body buffering. The CP model has not been evaluated for describing patients on mechanical ventilation.

The model of Wilson (86) provides a detailed description of fluid dynamics in the bronchial tree and pulmonary gas-exchange. A method for determining patient-specific model parameter describing pulmonary gas exchange is described. This model parameter i.e. '% lung damage' can be tuned from clinical data, however, it may be not provide the complexity required to describe heterogeneous $\dot{V}/\dot{Q}$ distributions seen in abnormalities of pulmonary gas exchange. Wilson's model includes a description of pulmonary gas-exchange, blood acid-base, pulmonary circulation and fluid dynamics of the bronchial tree, but not body buffering. Despite the level of complexity of this model, Wilson concluded that the description of patients on mechanical ventilation was not adequate for blood acid-base status and $FECO_2$ (86).

The model of Reynolds (87) provides a description of how inflammation of the lung tissue can alter pulmonary gas-exchange. There is no description of a method for determining patient-specific model parameters. Reynold's model parameters for pulmonary gas-exchange parameters have physiological interpretation, and are input by the researcher according to conditions of

interest. This model includes a description of pulmonary gas-exchange, blood acid-base, lung tissue buffer, and immune system, but not body buffering. Reynolds' model has not been evaluated to describe patients on mechanical ventilation, rather has been used to evaluate retrospectively and qualitatively data from typical patients.

The beat-to-beat model (88), is a physiological model capable of simulating changes in pulmonary gas-exchange, circulation, lung mechanics and the effects of positive ventilation on the circulatory system. A method for determining the values of patient-specific model parameters is described. This method includes an experimental procedure where fR is increased and reduced form the clinical value, until patients reach $FECO_2$ steady state. Continuous measurements of $FECO_2$ and $\dot{V}CO_2$ during the experimental procedure, cardiac output ($\dot{Q}$) are required to calculate the pulmonary gas-exchange model parameters. The beat-to-beat's parameters have physiological interpretation, model parameters describing pulmonary gas-exchange are: shunt fraction (fs); fraction of ventilation to alveolar compartment 1 (fA); and fraction of perfusion to compartment 1 (fQ). The beat-to-beat model includes a description of pulmonary gas-exchange, blood acid-base, pulsatile circulation and lung mechanics, but does not include a model of body buffering. The beat-to-beat model has been evaluated in patients on mechanical ventilation, and was shown to provide acceptable model predictions of $FECO_2$ (35).

The Evita weaning system (EWS) (89), is hybrid DSS, that integrates a rule-based and physiological models. There is no description of a method used for determining patient-specific model parameters. EWS includes a description of pulmonary gas-exchange and blood acid-base status, lung mechanics, but not body buffering. EWS has been evaluated in patients on mechanical ventilation model, and is was shown to provide adequate levels of ventilation support.

2.1.4. SUMMARY OF THE REVIEW

This section has reviewed models similar to INVENT's set of models. There are physiological models more complex than INVENT's set of models, which allow the simulation of the effects of inflammation, air flow in the bronchial tree, circulatory system and respiratory drive. However, no single model incudes extra complexity and at the same time can be identified from clinically available data. The majority of the models listed in table 2-1 were developed to simulate patient response with complex models, without the intention of inverting the models and performing parameter estimation.

A few of the models reviewed have functionality and complexity similar to INVENT, these being: 2C, NPS, SIVA-SOPAVent; Wilson's model, beat-to-beat, and EWS. SIVA-SOPAVent and EWS are hybrid DSS. For both systems, however, the interpretation of model parameters is not clear, and neither include a description of body buffering. The beat-to-beat and Wilson's models are similar to that of INVENT, with clear interpretation of model parameters. These models, however, do not include a representation of body buffering. The models 2C, and NPS are also similar to that of INVENT with a clear interpretation of parameters. These models describe all required model components (pulmonary gas-exchange, blood acid-base status and body buffering), however, models differ in the assumptions considered for describing each model component. For instance, INVENT's representation of bicarbonate distribution through a model of whole body buffering compares well to simulation of in-vivo blood-buffer curves (39,99,100). This model is necessary to describe the respiratory response of patients with abnormal blood acid-base status. The 2C model has been evaluated in animal models on mechanical ventilation, and COPD patients in conditions of hypoxia (90,101), NPS has been evaluated with virtual patients describing typical behavior of COPD and ARDS (36,93), the beat-to-beat model has been evaluated to simulate $FECO_2$ in ventilated patients (35), and the model of Wilson was evaluated in six patients on mechanical ventilation (86).

In conclusion, the set of models included in INVENT appears to be reasonable when considering the 7 criteria established at the start of this section. Model parameters can be tuned with clinically available data, at least with volumetric capnography and indirect calorimetry; model parameters have clinical interpretation; the set of models appears to have sufficient complexity, apart from the absence of a model of respiratory control; and models have been evaluated in laboratory and clinical conditions. The need of a respiratory control model is considered in the next sub-section.

2.1.5. MODEL REQUIREMENTS FOR DESCRIBING SPONTANEOUSLY BREATHING PATIENTS

Spontaneously breathing patients' response to changes in ventilator support depends upon different physiological processes. For instance, consider a patient being ventilated in PSV that is subjected to a reduction in PS. After reducing PS, there will be a dynamic response followed by a new steady state condition (30). The dynamic response will be an immediate reduction in VT, and total breathing time. The stready state response will be the increased ventilation that compensates for changes in blood acid-base status. These responses can be explained as a sequence of processes. After reducing PS, both inspired VT and the alveolar volume are reduced, since the respiratory system compliance is constant. In turn, changes in the alveolar volume

modify concentration of alveolar gases, the alveolar concentration of O_2 (FAO_2) decreases, and the alveolar concentration of CO_2 ($FACO_2$) increases. Accordingly, capillary, arterial and mixed venous pressures of O_2 decrease, and capillary, arterial and mixed venous pressures of CO_2 increase. Changes in blood O_2 and CO_2 are delayed due to blood circulation, washing in and washing out of CO_2 and bicarbonate distribution within body fluid compartments (blood, interstitial fluid, tissue water). Decreased PaO_2 reduces blood oxygen saturation, and increased $PaCO_2$, alters blood acid-base status, increasing $[H^+a]$ (reducing pHa and increasing $PaCO_2$). In turn, the respiratory chemoreflexes increase ventilation in response to increasing $[H^+a]$, $PaCO_2$ and PaO_2, typically by increasing the muscle generated pressure (Pmus) to increase VT. Increasing respiratory muscles activity may increase $\dot{V}O_2$, $\dot{V}CO_2$, and VT. The steady state ventilation results from the equilibrium between all of these processes.

The set of models included in INVENT describes the processes affecting changes in ventilation and blood acid-base status, taking into account the effects of bicarbonate distribution, the Bohr and Haldane effects, and changes in O_2 intake ($\dot{V}O_2$) and production of CO_2 ($\dot{V}CO_2$). In order to describe spontaneously breathing patients with INVENT's set of models requires the addition of a process describing the mechanism of chemoreflex response to $[H^+a]$ (or $PaCO_2$) that controls ventilation to regulate $[H^+a]$ and PaO_2. The next section presents and reviews several mechanisms describing chemoreflex control of ventilation i.e. models of respiratory control. The criteria for reviewing such models is based upon their potential applicability to describe individual patients' response to changes in the level of ventilator support at the bedside.

2.2. REVIEW AND SELECTION OF RESPIRATORY CONTROL MODELS

Several respiratory control models describing the mechanism that controls ventilation to regulate either arterial hydrogen ion concentration in the arterial blood ($[H^+a]$) or $PaCO_2$, and PaO_2, have been previously developed (102,103). This section presents a review of these models in the context of applying them at the bedside to describe patients' response to changes in ventilator support.

2.2.1. DESCRIPTION OF THE MECHANISM OF RESPIRATORY CONTROL

Figure 2-2 illustrates the chemoreflex mechanism that controls ventilation to regulate $[H^+a]$, and PaO_2, (103). This figure illustrates the feedback regulation

linking ventilation and acid-base status of blood and CSF (104). Ventilation is generated by the addition of three respiratory drives i.e. wakefulness, central chemoreflex and peripheral chemoreflex. Wakefulness drive does not depend on chemical inputs, and is considered the behavioral component of breathing. It is assumed to be zero during sleeping or unconscious breathing (105). Central and peripheral chemoreflex drives are generated at the central and peripheral chemoreceptors, respectively. Central chemoreceptors are located in the ventrolateral surface of the medulla oblongata (106,107). This type of chemoreceptors sense the hydrogen ion concentration in the cerebrospinal fluid (CSF) ([H^+csf]), which depends on $PaCO_2$ and the buffer capacity of the CSF (108,109). Central chemoreceptors generate the central chemoreflex respiratory drive as a function of [H^+csf]. Peripheral chemoreceptors are located in the carotid bodies (106,107). These chemoreceptors sense [H^+a], which depends on $PaCO_2$, and arterial blood acid-base status. The peripheral chemoreceptors generate the peripheral chemoreflex respiratory drive as a function of [H^+a], $PaCO_2$, which is modulated by the level of PaO_2 (103).

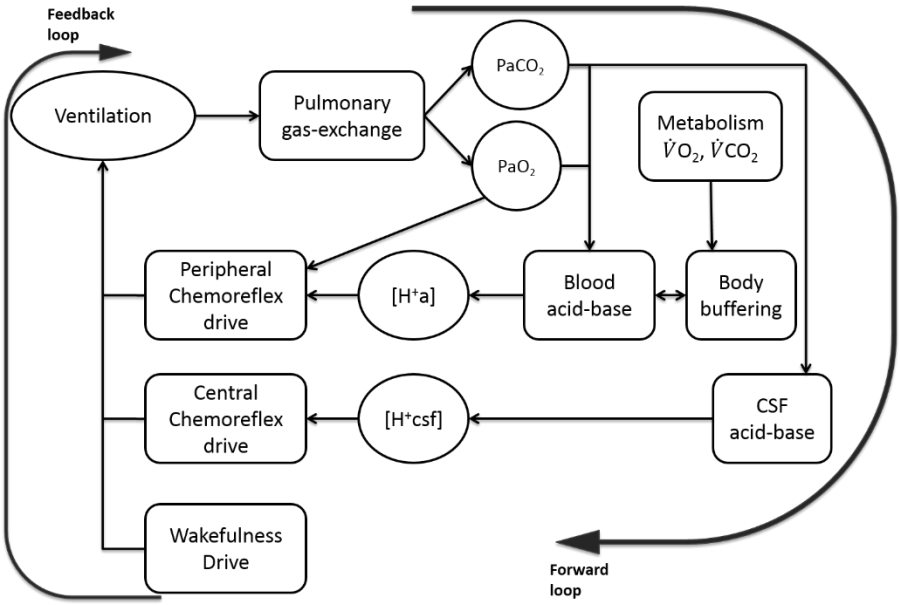

Figure 2-2. Block diagram describing the chemoreflex control of ventilation to regulate pHa or $PaCO_2$. Ventilation is produced as the addition of three respiratory drives i.e. wakefulness, peripheral chemoreflex, and central chemoreflex. The peripheral and central chemoreflex drives are generated by [H^+a] and [H^+csf], respectively. In

addition, the peripheral chemoreflex drive is sensitive to PaO_2. $[H^+a]$ and $[H^+csf]$ are dependent upon $PaCO_2$ and the acid-base status within arterial blood and CSF, respectively. PaO_2 and $PaCO_2$ depend upon the pulmonary gas-exchange conditions and ventilation.

The three respiratory drives described above result in ventilation or respiratory drive, which, depending upon FIO_2 and pulmonary gas-exchange, will result in changes in PaO_2 and $PaCO_2$. In turn, values of PaO_2 and $PaCO_2$, will result in arterial blood oxygen saturation and $[H^+a]$ which will depend upon patients blood acid-base status, including base excess (BE) and the characteristics of the oxygen dissociation curve. CO_2 molecules diffuse freely from arterial blood to CSF and the value of $[H^+csf]$ will therefore depend upon $PaCO_2$ and the buffer capacity of CSF (SIDcsf). These changes in acid-base status complete the feedforward loop with changes in $[H^+a]$, $[H^+csf]$, and PaO_2, signaling central and peripheral chemoreceptors.

Spontaneously breathing patients in assisted-ventilation modes, may present abnormal blood acid-base status, and increased $\dot{V}O_2$ and $\dot{V}CO_2$. Abnormal blood acid-base status, characterized by changes in BE, modifies the relationship between $PaCO_2$ and $[H^+a]$, altering the ventilation generated by the chemoreflex drives (104,110). To illustrate the effects of abnormal blood base excess (BE) in the respiratory response, figure 2-3 illustrates changes in ventilation on increasing $PaCO_2$ due to increasing inspired fraction of CO_2 ($FICO_2$), measured at three different blood acid-base conditions: normal (BE=0 mmol/l); metabolic acidosis (BE=-5 mmol/l); and metabolic alkalosis (BE=5 mmol/l). For normal conditions of blood acid-base (i.e. BE=0 mmol/l), ventilation increases linearly as $PaCO_2$ increases (solid line 'b' figure 2-3). For metabolic acidosis (i.e. negative values of BE), the respiratory response to increasing $PaCO_2$, is shifted to the left side from the normal blood acid-base response, so that, ventilation increases with lower $PaCO_2$ in comparison to normal blood acid-base (solid line 'a' in figure 2-3). Conversely, for metabolic alkalosis (i.e. positive values of BE), the respiratory response to increasing $PaCO_2$, is shifted to the right, so that, ventilation increases with higher $PaCO_2$ in comparison to normal blood acid-base (dashed line 'c' in figure 2-3). The solid lines were taken from (107) and the dashed line 'c' was taken from (11,12).

Increasing $FICO_2$ is an experimental procedure, which is not commonly performed in patients on mechanical ventilation. However, models ability to reproduce the effects of increased $FICO_2$ may imply that such models are likely to describe adequately changes in $\dot{V}CO_2$. Section 4.2.1 verifies the ability of the model of respiratory control integrated into INVENT's set of models to simulate abnormal blood acid-base states at two levels of $\dot{V}CO_2$.

In conclusion, $[H^+a]$, $[H^+csf]$, and PaO_2, determine ventilation generated by the chemoreflex drives. In addition, blood acid-base status, $\dot{V}O_2$, and $\dot{V}CO_2$ modulate ventilation generated by the chemoreflex drives, as illustrated in figure 2-3. A suitable respiratory control model for being integrated into INVENT's set of models, therefore, requires that both, peripheral and central drives, can describe the modulation effect of abnormal blood or CSF acid-base status, under different conditions of $\dot{V}O_2$, and $\dot{V}CO_2$.

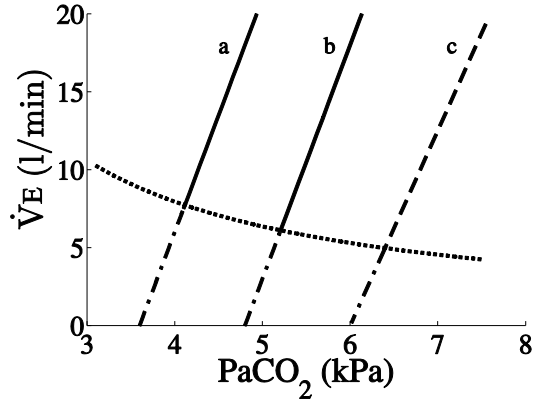

Figure 2-3. Respiratory response to increased $FICO_2$, during normal blood acid-base status, metabolic acidosis and metabolic alkalosis. The solid line 'a' illustrates the respiratory response to increasing $FICO_2$ in subjects with metabolic acidosis (BE=-5 mmol/l). The solid line 'b' illustrates the respiratory response to $FICO_2$ in subjects with normal blood acid-base status (BE=0 mmol/l). The solid line 'c' illustrate the respiratory response to increasing $FICO_2$ in subjects with metabolic alkalosis (BE=5 mmol/l). The dotted line represents the metabolic hyperbola, and the dot and dashed lines represent extensions of the respiratory response to $PaCO_2$.

Different respiratory control models have been developed to describe the chemoreflex mechanism controlling ventilation to regulate $[H^+a]$, PaO_2, and $[H^+csf]$ or $PaCO_2$ (102,103). The next sub-section describes criteria for reviewing such respiratory control models in regards to their capabaility to describe the modulation of ventilation according to blood and CSF acid-base disturbances, and their potential to be tuned with clinically available data. The aim of the review being to select a respiratory control model to describe patients' response to changes in the level of ventilator support.

2.2.2. CRITERIA FOR REVIEWING RESPIRATORY CONTROL MODELS

As mentioned in the previous sub-section, the selection of appropriate respiratory control models is essential for describing patients' respiratory

response to abnormal blood and CSF acid-base status and changes in $\dot{V}O_2$, and $\dot{V}CO_2$. The models are, therefore, reviewed with the following criteria:

1. Model parameters can be tuned with clinically available data and standard measurements available in the ICU (these being defined as measurement of ABG, volumetric capnography and/or indirect calorimetry).
2. Model parameters have physiological interpretation, and as such provide deeper understanding of patients' physiology.
3. Model complexity includes modulation of peripheral respiratory drive due to blood acid-base disturbances.
4. Model complexity includes modulation of central respiratory drive due to CSF acid-base disturbances.
5. Models have been adequately evaluated and shown to describe the respiratory response of healthy subjects or/and subjects with induced or pathological acid-base abnormalities.

The following sub-section reviews published respiratory control models, using these criteria.

2.2.3. REVIEW OF RESPIRATORY CONTROL MODELS

Table 2-2 summarizes this review of 14 published respiratory control models. All models were reviewed according to the criteria presented in 2.2.2, with the first column of table 2-2 listing the main authors of the models, and the rest of the columns representing a single criterion. Table cells of the second, third and last columns contain either 'yes' or 'no', denoting whether each model meets the requirement. The fourth and fifth columns list each model's input variables and parameters, respectively. The sixth column indicates whether each model includes additional model complexity.

The model of Lloyd (111) provides a description of the respiratory response to CO_2 in healthy subjects. Lloyd's model parameters can be tuned from clinical data and have physiological interpretation. To estimate ventilation the model requires $PaCO_2$ and PaO_2, but there is no description of modulation of the respiratory drive.

The model of Grodins (112), provides a description of the respiratory response to CO_2, including a mechanism to modulate ventilation via the CSF pH (pHcsf), and cerebral blood flow (CBF). Grodins' model parameters can be tuned from clinical data and have physiological interpretation. To estimate ventilation, the model requires $PaCO_2$, pHa, and pHcsf. The modulation of

ventilation is performed by varying CBF and changing the value of the parameter describing the relationship between pHa and pHcsf.

The model of Khoo (113) provides a description of the respiratory response to CO_2. Khoo's model parameters can be tuned from clinical data and have physiological interpretation. To estimate ventilation, the model requires $PaCO_2$, and PaO_2. The modulation of ventilation is performed by changing controller gains and time delay due to blood circulation.

The model of Longobardo (114) provides a description of periodic breathing at different metabolic rate conditions, the model includes a mechanism to modulate ventilation via CBF and body circulation. Not all model parameters can be tuned with clinical data, neither have physiological interpretation. To estimate ventilation, the model requires $PaCO_2$ and PaO_2. The modulation of ventilation can be performed by changing the values of time delay constants that modify body circulation and CBF.

The model of Yamamoto (115) provides a description of steady state ventilation during resting conditions and exercise. Also, this model tries to explain the mechanism of exercise hyperpnoea. Yamamoto's model parameters can be tuned from clinical data and have physiological interpretation. To estimate ventilation, the model requires $PaCO_2$. The modulation of ventilation is performed by varying the gradient between brain and arterial PCO_2.

The model of Ursino (116,117) provides a description of response to hypercapnia and hypoxia, also includes a mechanism to modulate ventilation via CBF and central ventilatory depression (CVD). Ursino's model parameters can be tuned from clinical data and have physiological interpretation. To estimate ventilation, the model requires $PaCO_2$ and PaO_2. The modulation of ventilation is performed by changing values of chemoreceptor gains and time delay due to blood circulation.

The model of Topor (118) provides a description of respiratory response to CO_2, and is focused on describing respiratory control instability e.g. Cheyenne-Stokes breathing (CSB). Topor's model parameters can be tuned from clinical data and have physiological interpretation. To estimate ventilation, the model requires $PaCO_2$, and PaO2. The modulation of ventilation is performed by changing values of chemosensitivity, and time delay due to blood circulation.

The model of Zhou (119) provides a description of respiratory response to CO_2, and includes a mechanism to modulate ventilation via CBF and CVD. Zhou's model parameters can be tuned with clinical data and have physio-

Table 2-2. Review of respiratory control models.

Autors	**Model parameters:**		**Model complexity**
	Can be tuned to individual patient with clinical data	Physiological interpretation	Blood variables driving the respiratory response
Lloyd (111)	yes	yes	$PaCO_2$, PaO_2
Grodins (112)	yes	yes	$PaCO_2$, pHa
Khoo (113)	yes	yes	$PaCO_2$, PaO_2
Longobardo (114)	yes	no	$PaCO_2$, PaO_2
Yamamoto (115)	yes	yes	$PaCO_2$
Ursino (116,117)	yes*	yes	$PaCO_2$, PaO_2
Topor (118)	yes	yes	$PaCO_2$, PaO_2

Table 2-2. Review of respiratory control models (continuation).

Autors	**Model complexity**		**Evaluation of the model in subjects with and without blood acid-base abnormalities.**
	Modulation of the respiratory drive	Others	
Lloyd (111)	no	---	no
Grodins (112)	pHcsf and via time delay constants	CSF acid-base, body circulation, CBF	no
Khoo (113)	via circulation delays, and controller gains	Cheyne-Stokes breathing	no
Longobardo (114)	via time delay constants	Body circulation, CBF, CO_2 and O_2 stores in the body	no
Yamamoto (115)	via $PbrainCO_2$, gradient arterial-brain CO_2	CBF, exercise hyperpnea	no
Ursino (116,117)	via chemoreceptor gains and circulation delay	CVD, CBF	no
Topor (118)	via chemosensitivity and time delay between lungs and chemoreceptors	Cheyne-Stokes breathing, body circulation	no

Table 2-2. Review of respiratory control models.

Autors	**Model parameters:**		**Model complexity**
	Can be tuned to individual patient with clinical data	Physiological interpretation	Blood variables driving the respiratory response
Zhou (119)	yes	yes	$PaCO_2$, PaO_2
Duffin (103)	yes	yes	pHa, $PaCO_2$, PaO_2
Anslie (102)	yes	yes	$PaCO_2$, PaO_2
Ben-Tal (81,120)	yes*	yes	$PaCO_2$, PaO_2
Poon (121)	yes	yes	$PaCO_2$
Albanese, Chbat (84,85)	yes	no	$PaCO_2$, PaO_2
Fowler (122)	yes	yes	$PaCO_2$, pHa

Table 2-2. Review of respiratory control models (continuation).

Autors	**Model complexity**		**Evaluation of the model in subjects with and without blood acid-base abnormalities.**
	Modulation of the respiratory drive	Others	
Zhou (119)	via chemosensitivity and time delay between lungs and chemoreceptors	CVD, CBF	no
Duffin (103)	via acid-base of CSF and blood	CSF acid-base	yes
Anslie (102)	via acid-base of CSF and blood	CBF, $PcsfCO_2$	yes
Ben-Tal (81,120)	via time delay between lungs and chemoreceptors	Neural rhythm generator, body circulation, CBF	no
Poon (121)	via chemoreceptor gains and time delay	Work of breathing	no
Albanese, Chbat (84,85)	via chemoreceptor gains and time delays	Body circulation, lung mechanics	no
Fowler (122)	via chemoreceptor gains and time delays	CBF, control of CSF buffering	no

logical interpretation. To estimate ventilation, the model requires $PaCO_2$ and PaO_2. The modulation of ventilation is performed by changing values of chemosensitivity and time delay between lungs and chemoreceptors due to blood circulation.

The model of Duffin (103) provides a description of respiratory response to CO_2, and includes a model of acid-base status of the CSF. Duffin's model parameters can be tuned with clinical data and have physiological interpretation. To estimate ventilation, the model requires pHa, $PaCO_2$ and PaO_2. The modulation of ventilation is performed by defining the acid-base status of the CSF. This model has been evaluated qualitatively against data from literature, and quantitatively against experimental conditions including increase in $FICO_2$, high altitude acclimation and hypoxia (110,123).

The model of Anslie (102) is an extension of Duffin's model. This model includes a mechanism to modulate ventilation via CBF, and a model for estimating the CSF partial pressure of CO_2 ($PcsfCO_2$). Anslie's model parameters can be tuned with clinical data and have physiological interpretation. To estimate ventilation, the model requires $PaCO_2$, and PaO_2. The modulation of ventilation is performed by defining the acid-base status of the CSF, which depends on CBF and $PcsfCO_2$. This model has been evaluated with an experimental protocol.

The model of Ben-Tal (81,120) provides a description of respiratory response to CO_2, this model includes a neural rhythm generator, and ventilation is modulated via the time delay between lungs and chemoreceptors. Ben-Tal's model parameters can be tuned with clinical data and have physiological interpretation. To estimate ventilation, the model requires $PaCO_2$ and PaO_2. The modulation of ventilation is performed by changing the values of time delay constants due to blood circulation.

The model of Poon (121,124) provides a description of respiratory response to CO_2, exercise hyperpnoea, and includes a model of work of breathing. Poon's model parameters can be tuned with clinical data and have physiological interpretation. To estimate ventilation, the model requires $PaCO_2$, and the relationship between dead space and tidal volume (VD/VT). The modulation of ventilation is performed by changing values of chemoreceptor gains, time delay constantans due to blood circulation, and VD/VT.

The model of Albanese-Chbat (84,85) provides a description of respiratory response to CO_2, body circulation and lung mechanics. This is a theoretical model developed to simulate patients on mechanical ventilation. Albanese-Chbat's model parameters can be tuned with clinical data, but not all the

parameters have clinical interpretation. To estimate ventilation, the model requires $PaCO_2$ and PaO_2. The modulation of ventilation is performed by changing values of chemoreceptor gains, and time constants due to blood circulation.

The model of Fowler (122) provides a description of respiratory response to CO_2, body circulation, CBF, and CSF buffering. Fowler's model parameters can be tuned with clinical data and have physiological interpretation. To estimate ventilation, the model requires $PaCO_2$, and pHa. The modulation of ventilation is performed by changing values of chemoreceptor gains and time constants due to blood circulation.

2.2.4. MODEL SELECTION

All the models of respiratory control listed in table 2-2 have parameters that can be tuned with clinical data, and all of them but two, use parameters that have physiological interpretation. In general, these model parameters are: time delay constants due to blood circulation, chemoreceptor sensitivity to either $PaCO_2$, or $[H^+a]$, and central and peripheral chemoreceptor gains. All the models but one, have the capacity of modulating the respiratory response, so that, several abnormal respiratory responses can be simulated.

The model of Duffin (103), has been previously evaluated against literature data and experimental data, and is the only model that includes an explicit model of acid-base status for the CSF. The advantage of using a CSF acid-base model is that, the central respiratory chemoreflex drive can be modulated by abnormal CSF acid-base status due to e.g. metabolic acidosis, rather than a selecting a certain value of chemoreceptor gain. The same advantage applies for arterial blood, in this case, the peripheral chemoreflex respiratory drive can be modulated due to blood acid-base disturbances. Besides Duffin's model, the models of Grodins (112) and Fowler (122) also require pHa to estimate the peripheral chemoreflex respiratory drive, and highlight the importance of estimating pHcsf for modulating the respiratory response to CO_2. However, only Duffin's model includes mass-action equations for determining the CSF acid-base status.

According to the review of respiratory control models, the model of chemoreflex control of breathing of Duffin includes a model of CSF acid-base status that can be used to modulate the respiratory response. For this reason, Duffin's model was selected to be integrated into INVENT's physiological models. The resulting model may describe spontaneously breathing patients in assisted ventilation. The next chapter describes the integration of the model of chemoreflex control of breathing into INVENT.

CHAPTER 3. INTEGRATION OF THE SELECTED MODEL OF RESPIRATORY CONTROL INTO INVENT'S SET OF MODELS

In the previous chapter, the model of respiratory control that will be integrated into INVENT's set of models was selected. To do so, a review of models of respiratory control was performed. In addition, the underlying assumption that INVENT's set of models adequately describes patient's response was validated, by reviewing physiological models similar those included in INVENT's set of models. The respiratory control model selected was the chemoreflex breathing control model of Duffin. This was selected due to its capability to describe respiratory response, and being potentially tuned for individual patients with clinical data. In order to integrate Duffin's model into the set of models included in INVENT, Duffin's model requires two modifications, these being: to describe the relationship between patients' blood and CSF acid-base status; and to allow disfacilitation of the respiratory drive due to abnormal blood or CSF acid-base status. In addition to integration of Duffin's model, two further modifications of INVENT's models were required for these models to describe spontaneous breathing. These are model representation of the situation where patients respond inadequately to changes in ventilator support, due to for example respiratory muscles failure, and the representation of respiratory mechanics in the situation of active breathing. This chapter describes the integration of Duffin's model into the INVENT's set of models, including the above mentioned modifications. Section 3.1 describes INVENT's physiological models and how model parameters are tuned to individual patients. Section 3.2 describes the model of chemoreflex breathing control, and the modifications performed to the model. Section 3.3 describes the quantification of muscle function, and section 3.4 describes the quantification of effective compliance. Model assumptions and limitations are listed in section 3.5.

3.1. DESCRIPTION INVENT'S SET OF PHYSIOLOGICAL MODELS

INVENT is a model-based DSS that provides patient-specific advice on ventilator settings in controlled ventilation modes. To do so, models parameters are tuned to individual patients' conditions. The models can then be used to perform a series of simulations describing the likely patient response to changes in ventilation, and advice is generated based upon the most optimal simulation results. The simulations are performed with the set of physiological models illustrated in figure 2-1. The use of physiological models to describe or simulate patients' response allows combining the effects of relevant physiological systems involved in ventilation (blood acid-base status, body buffering, and pulmonary gas-exchange). The set of physiological models has been evaluated retrospectively (2-4) and prospectively (5) to describe patients-response to changes in controlled-ventilation. The following subsections describe the models included in INVENT, i.e. those describing blood acid-base status, body buffering, and pulmonary gas-exchange.

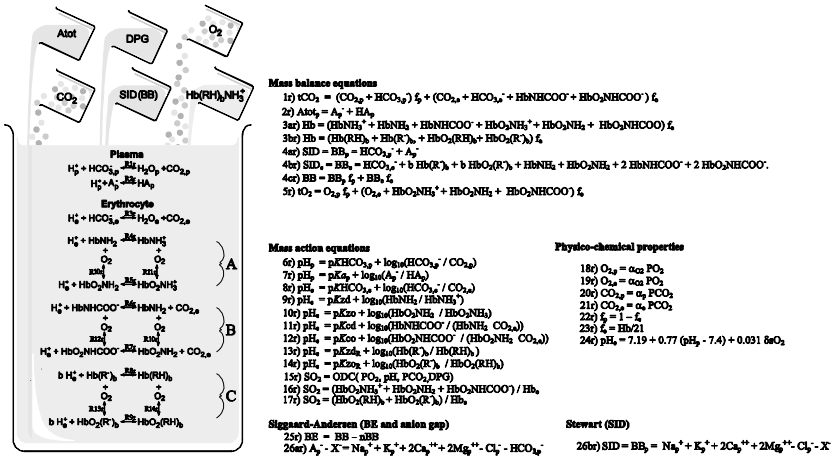

Figure 3-1. Model of blood acid-base status (38). (With kind permission from Springer Science+Business Media: Eur J Appl Physiol, Mathematical modeling of the acid–base chemistry and oxygenation of blood – A mass-balance, mass-action approach including plasma and red blood cells, 108, 2010, page 485, Rees SE, Klæstrup E, Handy J, Andreassen S, Kristensen SR, figure 1B.)

3.1.1. BLOOD ACID-BASE STATUS MODEL

The model of blood acid-base status, illustrated in Figure 3.1, includes six blood components: O_2; CO_2; hemoglobin ($Hb(RH)_3NH_3^+$); plasma non-bicarbonate buffer (NBB); buffer base (BB) or strong ion difference (SID); and concentration of 2,3 diphosphoglycerate (DPG) (37). The relationship between these components is given by 26 equations (37,38), including mass-balance and mass-action equations, and physico-chemical properties of blood, as illustrated in figure 3-1. This model of blood acid-base chemistry describes acid-base and oxygenation of red blood cells, and a formulation of the oxygen dissociation curve describing the Bohr and Haldane effects (125-127). The 26 equations can be solved with data from a single arterial blood gas measurement (pHa, PaO_2, $PaCO_2$, Hb, SaO_2), to determine the blood acid-base model parameters base excess (BE or buffer base-normal buffer base) and DPG (37).

3.1.2. BODY BUFFERING MODEL (WHOLE BODY O_2-CO_2 TRANSPORT AND STORAGE)

The model of body buffering describes O_2 and CO_2 transport from the lungs to the tissues and vice-versa, considering CO_2 storage in interstitial fluid and tissue water (figure 3-2). The model was designed to describe the effects of abnormal $\dot{V}O_2$ and $\dot{V}CO_2$, which alter the equilibrium (homeostasis) between ventilation, and the acid-base status of arterial blood, mixed venous blood, interstitial fluid and tissue water. To do so, the model includes 45 equations (39) describing acid-base chemistry and mass conservation within the interstitial fluid and tissue water, taking into account $\dot{V}O_2$ and $\dot{V}CO_2$, cardiac output ($\dot{Q}$). These equations are combined with the model of blood acid-base status to describe arterial and mixed venous blood (39). At steady state, the body buffering model determines the content of CO_2 stored in the interstitial fluid and tissue water, and hence the distribution of bicarbonate [HCO_3^-] between blood, interstitial fluid and tissue compartments. This model is necessary to describe and simulate the in-vivo equilibration curves for the relationship between [$HCO_{3\,a}^-$] and $PaCO_2$ (39,99,100).

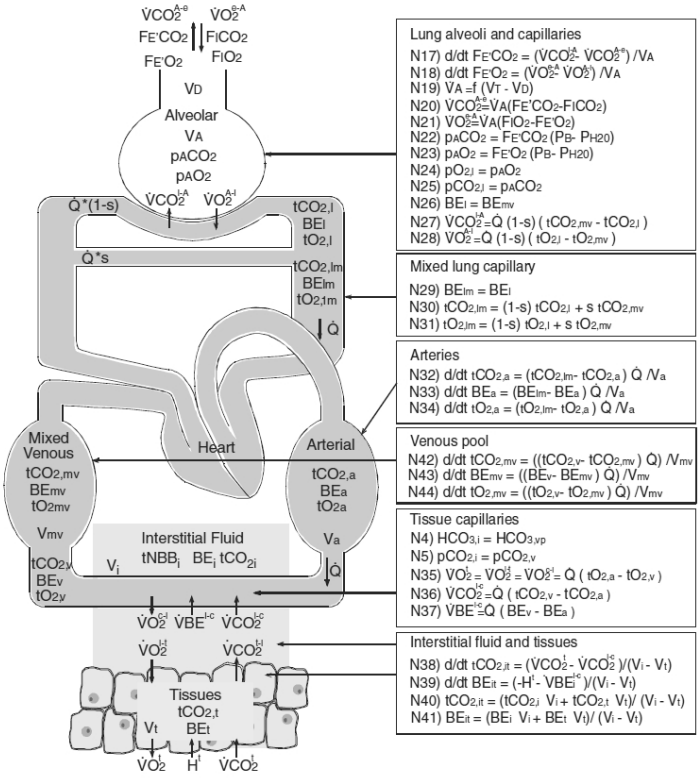

Figure 3-2. Model of body buffering (whole body O2 and CO2 transport and storage). Reproduced from (39) with kind permission of Begell House Inc.

3.1.3. PULMONARY GAS-EXCHANGE MODEL

The model of pulmonary gas-exchange describes the effects of serial dead space (Vds), shunt fraction (fs), and mismatch of the lung's ventilation-perfusion ($\dot{V}/\dot{Q}$) distribution on blood acid-base status (figure 3-3). The model consists of four compartments, two ventilated and perfused compartments, a shunted compartment, and a serial dead space compartment. Two sets of 10 equations each, are used for describing delivery of O_2 ($\dot{V}O_2$)and removal of CO_2 ($\dot{V}CO_2$), respectively (40), as illustrated in figure 3-3. The pulmonary gas-exchange model equations require simultaneous solution with the models of blood acid-base, and body buffering. The three model parameters are shunt fraction (fs), fraction of alveolar ventilation ventilating the second alveolar-compartment (fA2), and fraction of non-shunted blood perfusing the second

alveolar-compartment (f2). The model parameters are estimated with an experimental procedure in which FIO_2 is modified in 3-5 step changes. The corresponding measurements of pulse oximetry (SpO_2), FIO_2, end tidal O_2 (FeO_2), end tidal CO_2 ($FECO_2$), $\dot{V}O_2$, $\dot{V}CO_2$ taken at each FIO_2 step change, and a single arterial blood gas (ABG) measurement taken at the beginning of the experimental procedure, are required for parameter estimation (61,128). The model determines the relationship between end tidal gases and arterial blood pressures for given inspired gases (FIO_2, $FICO_2$), $\dot{V}CO_2$, $\dot{V}O_2$ and Vds. The pulmonary gas-exchange model has been applied in a number of clinical studies (2-5) and has been evaluated against the reference technique for determining gas-exchange (i.e. MIGET) in both homogeneous and heterogeneous lung models (129,130).

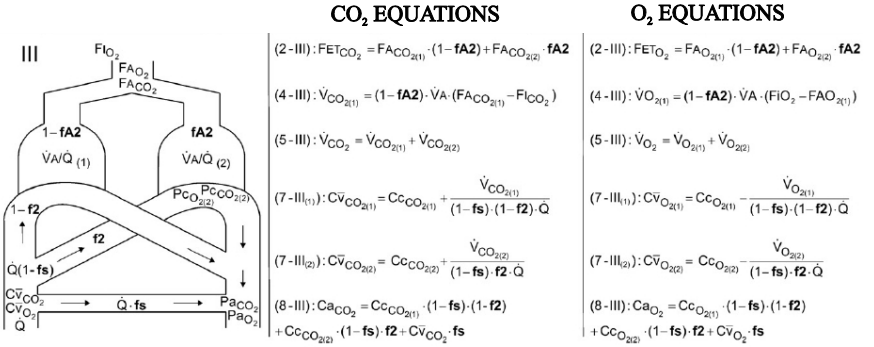

Figure 3-3. Model of pulmonary gas-exchange (40). Reprinted from Medical Engineering and Physics, 33, Karbing DS, Kjaergaard S, Espersen K, Rees SE. Minimal model quantification of pulmonary gas exchange in intensive care patients, 240-248, Copyright (2011), with permission of Elsevier.

Figure 3-4 illustrates a complete picture of the models included in INVENT (figure 3-4 A-C). The components of the respiratory control model (figure 3-4 D-E), and the descriptions of muscle function (figure 3-4 F), and effective compliance (figure 3-4 G), are also included. These components represent the added modelling complexity of this PhD thesis, and their details are explained in the following sections.

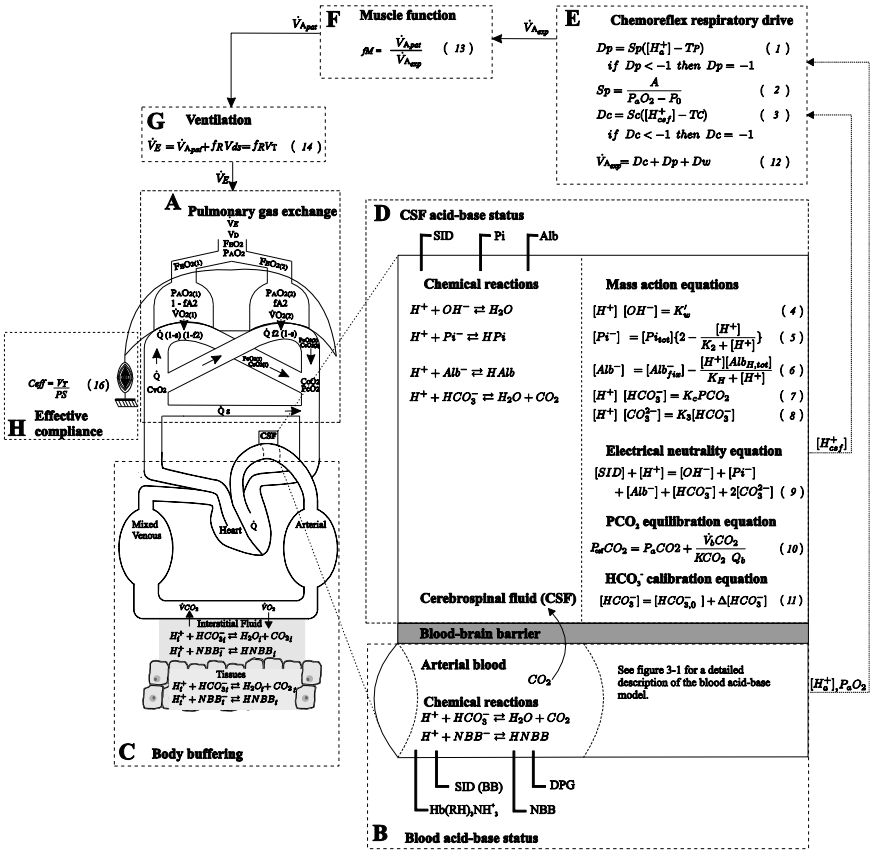

Figure 3-4. Structure of the set of physiological models describing patients' response to changes in the level of ventilator support. The set of model includes: pulmonary gas-exchange (A); blood acid-base status (B); body buffering (whole body O_2 and CO_2 transport and storage) (C); cerebrospinal fluid (CSF) acid-base status (D); chemoreflex respiratory drive (E); muscle function (F); ventilation (G); and effective compliance (H).

3.2. CHEMOREFLEX BREATHING CONTROL MODEL

The chemoreflex breathing control model of Duffin (103) determines the ventilation as the addition of three respiratory drives (Figure 3-4E), these being peripheral and central respiratory chemoreflex drives, and a behavioral drive (wakefulness drive). The peripheral and central chemoreflex drives are dependent upon $[H^+]$ sensed at the carotid bodies and medulla oblongata, respectively. The wakefulness drive is considered a constant input,

depending upon the patients' state of consciousness. The model of Duffin was modified to be integrated into INVENT's set of models in the following ways: to represent the inhibition of the chemoreflex respiratory drives due to metabolic blood acid-base compensation, as often occurs in chronic obstructive pulmonary disease (COPD) (101); to modify CSF acid-base status according to blood acid-base status; and to calibrate the values of constants in Duffin's models such that the normal values of the peripheral and central thresholds to $[H^+]$ were calculated to match the normal values of blood acid-base status simulated using INVENT's set of models . The following sub-sections describe the components of Duffin's model, and the corresponding modifications. The description of the calculation of the normal values of the peripheral and central thresholds is in the next chapter.

3.2.1. PERIPHERAL CHEMOREFLEX DRIVE

Equation 1 describes the peripheral chemoreflex drive as a function of the arterial hydrogen ion concentration ($[H^+a]$), where Sp is the peripheral sensitivity to $[H^+a]$, TP is the peripheral threshold, and Dp is the peripheral drive. Sp is modulated by PaO_2 as defined in Equation 2, where *A=2.373 l kPa/(min nM/l)* and P_0*=4 kPa*. Duffin's model was modified by adding a condition, which allows disfacilitation (or down-regulation) of ventilation, so that, Dp can reduce ventilation up to *-1 l/min*. As such, Dp can reduce ventilation when $[H^+a]$ is lower than TP. This situation can be due to e.g. abnormal blood acid-base status, hyperventilation or reduced $\dot{V}CO_2$ (131-133). Describing disfacilitation of ventilation through Dp is therefore necessary to describe patients in assisted ventilation.

$$Dp = Sp\ ([H_a^+] - TP) \qquad (1)$$
$$if\ Dp < -1\ then\ Dp = -1$$

$$Sp = \frac{A}{P_aO_2 - P_0} \qquad (2)$$

In order to determine Dp, the following variables are required $[H^+a]$ and PaO_2, which are determined with the model of blood acid-base status from INVENT's set of models.

3.2.2. CENTRAL CHEMOREFLEX DRIVE

Equation 3 describes the central chemoreflex drive as a function of the CSF hydrogen ion concentration ($[H^+csf]$), where Sc is the central sensitivity to $[H^+csf]$, TC is the central threshold, and Dc is the central drive. Duffin's model was modified by adding a condition, which allows disfacilitation (or down-

regulation) of ventilation, so that, Dc can reduce ventilation up to *-1 l/min*. As such, Dc can reduce ventilation when [H^+csf] is lower than TC. This situation can be due to e.g. abnormal CSF acid-base status, change in the state of consciousness, increase in cerebral blood flow, hyperventilation, or reduced $\dot{V}CO_2$ (131-135). Describing disfacilitation of ventilation through Dc is therefore necessary to describe patients in assisted ventilation.

$$Dc = Sc\left(\left[H^+_{csf}\right] - TC\right) \quad (3)$$
$$if\ Dc < -1\ then\ Dc = -1$$

In order to determine Dc, the variable required is [H^+csf], which is determined with the CSF acid-base model described in the next sub-section.

3.2.3. CSF ACID-BASE MODEL

The model of CSF acid-base status is illustrated in Figure 3-4D. This model describes CSF with four components: PCO_2, strong ion difference (SIDcsf), and concentration of phosphate (Pi) and albumin (Alb). The equations of the CSF acid-base model (equations 4-9) were taken from Duffin's model (103). The calculation of the CSF partial pressure of CO_2 ($PcsfCO_2$) was taken from (102) (equation 10), which is an extension of Duffin's model. Equation 10 allows the estimation of $PcsfCO_2$ from $PaCO_2$, and constant values of brain metabolism $\dot{V}bCO_2$, cerebral blood flow ($\dot{Q}b$) and the dissociation constant of CO_2 (KCO_2). The values of the constants are listed in table 3-1. The model of CSF acid-base status was modified with the addition of equation 11, which allows estimating CSF bicarbonate concentration ([HCO_{3^-csf}]) from individual patients' estimated mixed-venous blood bicarbonate concentration ([$HCO_{3,0}^-$]) (136). Estimating [HCO_{3^-csf}] is necessary to calculate SIDcsf, which determines the relationship between $PscfCO_2$ and [H^+csf], and hence, Dc. Alterations in SIDcsf due to abnormal blood BE due to metabolic compensation of either acidosis or alkalosis, result in changes in ventilation (11,12,108,109).

$$[H^+][OH^-] = K'_w \quad (4)$$
$$[Pi^-] = [Pi_{tot}]\left\{2 - \frac{[H^+]}{K_2 + [H^+]}\right\} \quad (5)$$
$$[Alb^-] = \left[Alb^-_{fix}\right] - \frac{[H^+][Alb_{H,tot}]}{K_H + [H^+]} \quad (6)$$
$$[H^+][HCO_3^-] = K_c PCO_2 \quad (7)$$
$$[H^+][CO_3^{2-}] = K_3[HCO_3^-] \quad (8)$$
$$[SID] + [H^+] = [OH^-] + [Pi^-] + \cdots$$

$$[Alb^-] + [HCO_3^-] + 2[CO_3^{2-}] \quad (9)$$

$$PCO_2 = PaCO_2 + \frac{\dot{V}bCO_2}{KCO_2\,\dot{Q}b} \quad (10)$$

$$\left[HCO^-_{3,csf0}\right] = \left[HCO^-_{3,0}\right] + \Delta[HCO_3^-] \quad (11)$$

In order to determine [H⁺csf] and SIDcsf, the variables required are $PaCO_2$ and $[HCO_{3,0}^-]$, which are determined with the model of blood acid-base status from INVENT's set of models. The importance of estimating [H⁺csf] is to calculate Dc, conversely, the importance of estimating SIDcsf is to simulate the effects of changing $PaCO_2$ on Dc. SIDcsf is considered constant because ion-exchange between blood and CSF is restricted due to the blood-brain barrier. As CO_2 molecules can pass across this barrier, [H⁺csf] can estimated from $PaCO_2$ (102,107).

Table 3-1. Constants of the CSF acid-base model.

Symbol	Name	Value
K_w	Ion product for water	$2.39\ x10^{-14}$
K_c	Combined CO_2 equilibrium and solubility	$2.45\ x10^{-11}$
K_3	Carbonate dissociation	$1.16\ x10^{-10}$
K_2	Phosphoric acid dissociation constant	$2.19\ x\ 10^{-7}$
K_H	Histidine dissociation constant	$1.77\ x10^{-7}$
KCO_2	CO_2 Dissociation constant (*ml/(ml kPa)*)	*0.0375*
$[Alb^-_{Fix}]$	Albumin fixed negative charge concentration (*mM/l*)	*3.95*
$[Alb^-_{H,tot}]$	Albumin concentration of histidine residues (*mM/l*)	*3.01*
$[Pi_{tot}]$	Phospahte concentration (*mM/l*)	*0.61*
$\dot{V}bCO_2$	Brain production of CO_2 (*ml (min/100gr)*)	*3*
$\dot{Q}b$	Brain blood flow (*ml (min/100gr)*)	*55*
$\Delta[HCO^-_3]$	CSF bicarbonate calibration factor (*mmol/l*)	*0.12*

In addition, an equation combining the three respiratory drive components is required to calculate the expected alveolar ventilation (V̇Aexp). Equation 12 represents V̇Aexp as the sum of the peripheral (Dp), central (Dc), and wakefulness drives (Dw). The values of Dw depend upon the state of consciousness of the patient, with *Dw=0 l/min* for sleeping or unconsciousness (105), and *Dw=2 l/min* for awaken patients. The latter Dw value was assumed to describe patients are calmly breathing, implying that Dw is not the major drive during spontaneous ventilation.

$$\dot{V}A_{exp} = Dp + Dc + Dw \quad (12)$$

So far, INVENT's set of models and the model of chemoreflex breathing control were described. The model of respiratory control can be used to calculate $\dot{V}A_{exp}$ from two chemoreflex respiratory drives (Dp and Dc), and Dw. Considering Dw as a constant depending upon the patients' state of consciousness, $\dot{V}A_{exp}$ can be calculated requiring four input variables from INVENT's set of models i.e. $[H^+a]$, PaO_2, $PaCO_2$ and $[HCO_{3,0}^-]$. The following sections describe the remaining model components, which are necessary to describe spontaneously breathing patients in assisted ventilation.

3.3. MODEL FOR QUANTIFYING MUSCLE FUNCTION

The chemoreflex breathing control model described above enables simulation of the expected alvelor ventilation ($\dot{V}A_{exp}$) due to chemoreceptor response. However there may be situations where following reduction of ventilator support patients cannot respond adequately to meet the chemoreflex driven ventilation, due to, perhaps, reduced muscle strength and endurance. In this situation, it is typical that $\dot{V}A$ falls, and hence, blood acid-base status changes, resulting in lower values of pHa and higher $FECO_2$. In order to describe this situation, a model of muscle function was required to describe patients' response to changes in the level of ventilator support. The quantification of muscle function model describes the difference between $\dot{V}A$ determined by the respiratory control model ($\dot{V}A_{exp}$) and the current measured $\dot{V}A$ generated by the patient ($\dot{V}A_{pat}$) (Figure 3-4F). Reduction of $\dot{V}A$ after reduction of ventilator support, has been described as fatigue or lack of strength of the respiratory muscles to generate Pmus (17,21,31). On reduction of ventilator support, patients' inability to satisfy $\dot{V}A_{exp}$ was, therefore, interpreted as fatigue, lack of strength or respiratory muscle failure.

Considering that patients are likely to maintain a preferred level of pHa (and $FECO_2$) (41,42), and assuming that the respiratory control model generates $\dot{V}A_{exp}$ that is required to maintain patients' preferred pHa. Then, the difference between $\dot{V}A_{exp}$ and $\dot{V}A_{pat}$ can be quantified as a ratio. Equation 13 describes the ratio between $\dot{V}A_{pat}$ and $\dot{V}A_{exp}$. This ratio was postulated as an indicator of the degree of patient response or muscle function (fm). A value of fM= 1 indicates that a patient responds according to their respiratory chemoreflex drive without any limits imposed by muscle function. After a step reduction in the level of ventilator support, values of fM<1 indicate reduced $\dot{V}A_{pat}$, in comparison to the respiratory chemoreflex drive, perhaps due to inadequate patient response. Conversely, after increase in ventilator support, values of fM>1 indicate increased $\dot{V}A_{pat}$ in comparison to chemoreceptor drive, perhaps due to patients being ventilated with level of ventilator support

which was too low, such that respiratory muscle could be more effectively used at higher levels.

$$fM = \frac{\dot{V}A_{pat}}{\dot{V}A_{exp}} \quad (13)$$

V̇Apat can be estimated from substituting Vds from equation 15 in equation 14, describing minute ventilation (V̇E).

$$\dot{V}E = VT * fR = \dot{V}Apat + (Vds * fR) \quad (14)$$

$$Vds = \frac{\dot{V}CO_2}{fR\,(VT\,(FECO_2 - FICO_2))} \quad (15)$$

The use of fM to describe patients' response to changes in the level of ventilator support will be presented in chapters 5 and 6, accounting for changes in VT and PS, respectively. The following section describes the quantification of patient effort.

3.4. MODEL FOR QUANTIFYING CHANGES IN EFFECTIVE COMPLIANCE DURING ASSISTED VENTILATION

In assisted ventilation, V̇E depends upon patients' effort and the level of ventilator support. Quantifying the contribution of patients' effort to V̇E is therefore necessary to describe patients' response to changes in the level of ventilator support. During PSV, VT results from patient effort, the level PS and the respiratory system mechanical characteristics (30,137,138). Thus, the ratio between VT and PS, i.e. effective compliance (Ceff) illustrated in figure 3-4 H, might be used to quantify changes in patient effort as PS is modified. The values of Ceff can be interpreted as follows: Ceff <0.05 l/cm H_2O, may indicate over-support, as VT might be mostly explained by the level of ventilator support (PS) and respiratory system mechanics (58); and Ceff >0.05 l/cm H_2O, may indicate that patient contributes to VT through substantial patient effort, as VT cannot be explained by accounting the level of ventilator support (PS) and respiratory system mechanics alone, and therefore these values probably reflect some patient effort. Equation 16 describes Ceff as the ratio between VT and PS in spontaneously breathing patients on mechanical ventilation.

$$Ceff = \frac{VT}{PS} \quad (16)$$

Ceff may be able to describe patient effort and can be measured readily at the bedside. Despite this, it may be a gross simplification the calculation of

patient effort (Pmus) and respiratory system mechanics. In chapter 6 the use of Ceff will presented for describing patients effort during mofication in PS levels.

3.5. MODEL ASSUMPTIONS AND LIMITATIONS

The model of respiratory control includes a large number of assumptions, which require consideration. The model describes steady state ventilation, for conditions of oxygenation and acid-base status. The model determines $\dot{V}A_{exp}$ form three respiratory drives, Dc, Dp and Dw. Dc depends upon $[H^+csf]$, which in turn is dependent upon SIDcsf and cerebral blood flow. Acute changes in these variables may alter Dc. SIDcsf is estimated from mixed venous blood bicarbonate, then is considered constant. Cerebral blood flow can change due to alterations in $[HCO_3^-a]$ or $PaCO_2$, and this variation is not included in the model. Dp depends upon $[H^+a]$, and PaO_2. $[H^+a]$ which depends upon blood acid-base status, and PaO_2 depends upon FIO_2 and blood oxygenation. Thus, acute changes blood acid-base and oxygenation status may alter Dp. Dw is dependent upon patients' state of consciousness, and behavior. Conditions of stress or pain may alter Dw, however, changes in Dw are not included in the model. In addition, the respiratory control model can be unstable i.e. steady state cannot be reached, under certain conditions. For example, conditions of low $\dot{V}CO_2$, increased cerebral blood flow or abnormal CSF acid-base status, can lead to instability of respiratory control. For these conditions a model of steady state conditions, such as that presented here, might be inadequate.

The model for quantification of muscle function assumes that the ventilation at baseline conditions is adequate, and is considered as reference. In conditions where respiratory muscles are responding adequately, then, $\dot{V}A_{pat}$ is equal to $\dot{V}A_{exp}$. There are, however, conditions that may alter $\dot{V}A_{pat}$ such as fatigue, respiratory muscles failure, reduced strength or endurance, anxiety or pain. This description cannot identify the cause of altered $\dot{V}A_{pat}$.

These respiratory control model assumptions will be returned in the discussion (section 7.3.1) in the context of the necessity of simplifying the model, in order to develop a clinical application sufficient to describe and simulate patients' response to changes in ventilator support.

The model of pulmonary gas-exchange assumes 4 ventilated compartments, and hence does not have the descriptive power of the 50 compartmental model used in the reference technique (64). The blood acid-base chemistry model does not include a description of electrolyte balance, which may be necessary for the description of fluid replacement therapy (139). Both blood

acid-base and pulmonary gas-exchange models assume constant cardiac output ($\dot{Q}$), which is seldom measured. In some circumstances it might be reasonable to estimated values if $\dot{Q}$ from the body surface area (4).

In the context of this work, applying models of ventilation, pulmonary gas-exchange, and blood acid-base and oxygenation, to describe patient response requires tuning all model parameters. To do so, measurements of $\dot{Q}$, $\dot{V}O_2$, $\dot{V}CO_2$, arterial blood gas analysis and an experimental procedure where FIO_2 is modified in 3-5 step changes are necessary. These measurements will be returned in the discussion (section 7.3.2) as practical limitations when performing the clinical study.

The model for quantification of changes in Ceff, assumes that the relationship between VT and PS may describe changes in patient effort. This assumption implies a gross description of patient effort and respiratory system mechanics. The interpretation of Ceff is further limited since there were no measurements of esophageal pressure, so Pmus or work of breathing are not available. The measurement of Ceff will be returned in the discussion (section 7.3.2) as a practical limitation when performing the clinical study.

3.6. CONCLUSION

This chapter has described the integration of physiological models to describe patient's response to changes in the level of ventilator support. For this purpose, two previously published models were integrated. The model of chemoreflex breathing control was integrated into the set of models included in INVENT, which previously described pulmonary gas-exchange, blood acid-base status and body buffering. The model of respiratory control has two model components (figure 3-4 D-E) i.e. CSF acid-base and respiratory control. Both model components were modified in order to describe spontaneously breathing patients in assisted ventilation. The CSF acid-base model required an equation to determine SIDcsf from the current blood acid-base status. The respiratory control equations required the addition of two conditions that allow the disfacilitation (down-regulation) of ventilation, which can result due to conditions of abnormal blood and CSF acid-base status.

In addition, two models were required to complete the description of spontaneously breathing patients' response: quantification of muscle function; and quantification of effective compliance. These two models allow to consider the situation of reduction of $\dot{V}A_{exp}$ due e.g. to respiratory muscles failure, and the increase of patient effort as PS is modified, respectively.

Before applying this set of models to simulate patients' response to changes in support ventilation, there are three additional requirements: estimation of the normal values of the respiratory control model parameters (TP and TC); identification of the patient-specific model parameters that describe patient response; and description of a method to calculate the values of such parameters. The following chapter describes these three requirements. The application of this set of models to describe patient response is described in chapters 5 and 6.

CHAPTER 4. SENSITIVITY ANALYSIS AND IDENTIFICATION OF MODEL PARAMETERS

The integration of the respiratory control model into INVENT's set of models was described in the previous chapter. Two additional models were also integrated, with these describing changes in: $\dot{V}A$ due to muscle function; and effective compliance (Ceff) due to patient effort and mechanics of the respiratory system. Describing patients' respiratory response through physiological models requires that models' parameters can be tuned to individual patients' data. This is done by determining which parameters describe patient-specific response, and determine a method for estimating values of these patient-specific parameters (140).

An overview describing the model parameters of the existing INVENT models, and their estimation has been presented in section 3.1. This chapter deals with the parameters of the respiratory control model. The models describing and quantifying muscle function (fM) and effective compliance (Ceff) do not require tuning since are measurements of patient performance, and their values are calculated as explained in sections 3.3-3.4. The parameters of the respiratory control model have been listed in section 3.2. However, neither the effect of these parameters on model simulations nor the estimation of values of these parameters to individual patient's data has been described.

This chapter describes the effect of modifying the respiratory control model parameters on simulated patients' responses under different conditions. In doing so, the necessary patient-specific parameters are identified, and a method for their estimation is proposed. For that purpose, in section 4.1 the normal values of the respiratory control model parameters TP and TC are estimated. To determine the appropriate patient-specific parameters, section 4.2 presents two series of model simulations, each corresponding to a group of factors that modify simulated patients' response ($\dot{V}Aexp$). $\dot{V}Aexp$ can be modified by either directly measured factors (describing blood acid-base status and metabolism) or indirectly measured factors (respiratory control). The first series of model simulation of $\dot{V}Aexp$ were performed varying two different directly measured factors (BE and $\dot{V}CO_2$). The second series of model simulation of $\dot{V}Aexp$ were performed at different conditions of BE and $\dot{V}CO_2$ varying each respiratory control model parameter, i.e. a sensitivity

analysis. Following this sensitivity analysis it was possible to identify which patient-specific model parameters were important and identifiable, and a single was selected as that to be tuned from clinical data. Section 4.3 describes the method for estimating patient-specific model parameters to individual patients using clinically available data.

For the complete set of models describing respiratory drive (i.e INVENT's set of models including models of respiratory control, quantification of fM, and quantification of Ceff) to be useful, they need to be evaluated in the clinical setting. Section 4.4 describes two clinical protocols that were designed to evaluate the ability of the set of models to describe patient's response to changes in ventilator support, and hence, to evaluate the integration of the model of respiratory control into the set of INVENT models.

4.1. DETERMINATION OF NORMAL VALUES OF TP AND TC

To perform simulations using the set of models describing respiratory drive, it is first necessary to determine the normal values of TP and TC that describe normal typical conditions of blood acid-base status and ventilation at steady state. Previously, values of TP and TC have been reported (102,103). However these values were determined to fit the model of respiratory breathing control to the normal subjects being studied. In addition, these subjects were spontaneously breathing without mechanical ventilation, and through a device designed to increase $FICO_2$ at several levels of FIO_2. Thus, physiological conditions of these subjects may differ from normal typical values of blood acid-base. In contrast, Sp and Sc are the slopes of the linear increase in ventilation due to increasing arterial or CSF $[H^+]$. These slopes are similar among subjects (13,107), and hence values of Sc and Sp were assumed to be constant (90). The normal values of variables included in INVENT's models of blood acid-base, pulmonary gas-exchange and body buffering are reported in table 4-1 (39). In addition, the normal values of SIDcsf and Dw were determined as *SIDcsf=31 mmol/l* (103) and *Dw=0 l/min*.

The normal values of TP and TC were estimated as follows. Normal values of $PaCO_2$ and SIDcsf, were used to solve the CSF acid-base model to determine a normal value of $[H^+csf]$. Peripheral and central chemoreflex respiratory drives (equations 17 and 18) were calculated from $[H^+a]$ and $[H^+csf]$ respectively, with normal values of Sp, Sc, and $[H^+a]$ calculated from normal pHa. To do so the normal values of Sp and Sc were taken from (103). The value of normal alveolar ventilation (*4.2 l/min*) was equated to the sum of Dp and Dc (equation19). As equation 19 is undetermined, in order to determine TP and TC a condition describing the normal operating point of the

system (118) was included (equation 20). The solution of equations 19 and 20 resulted in the normal values of TP (*TP=37.75 nmol/l*) and TC (*TC=45.24 nmol/l*).

Table 4-1. Typical normal conditions of blood acid-base status, pulmonary gas-exchange, ventilation and respiratory control.

Symbol	Name	Value
Blood acid-base, body buffering and ventilation		
FIO_2	Inspired fraction of O_2	*0.208*
$FICO_2$	Inspired fraction of CO_2	*0.003*
$\dot{V}A$	Alveolar ventilation (*l/min*)	*4.2*
$\dot{V}CO_2$	CO_2 production (*ml/min*)	*0.222*
$\dot{V}O_2$	O_2 consumption (*ml/min*)	*0.253*
$\dot{Q}$	Cardiac output (*l/min*)	*5*
BEa	Arterial base excess (mmol/L)	*0*
pHa	Arterial pH	*7.4*
PaO_2	Arterial partial pressure of O_2 (*kPa*)	*12.15*
$PaCO_2$	Arterial partial pressure of CO_2 (*kPa*)	*5.35*
$[HCO_{3,0}^-]$	Mixed-venous bicarbonate concentration (*mmol/l*)	*26.3*
Hb	Hemoglobin concentration (*mmol/l*)	*9.3*
DPG	2,3 diphosphoglycerate (*mmol/l*)	*5*
Pulmonary gas exchange model parameters		
s	Pulmonary shunt (*%*)	*5*
f2	Fraction of non-shunted perfusion to compartment 2	*0.9*
fA2	Fraction of alveolar ventilation to compartment 2	*0.9*
Vds	Serial dead space (*l*)	*0.15*
Chemoreflex respiratory drive model parameters		
Sc	Central sensitivity (*l/min/(nmol/l)*)	*1.78*
Sp	Peripheral sensitivity (*l/min/(nmol/l)*)	*0.29*
TC	Central threshold (*nmol/l*)	*45.24*
TP	Peripheral threshold (*nmol/l*)	*37.75*
SIDcsf	CSF strong ion difference (*mmol/l*)	*31*
Dw	Wakefulness drive (*l/min*)	*0*

$$Dp_{normal} = 0.29 * (39.78 - TP) \quad (17)$$
$$Dc_{normal} = 1.78 * (47.27 - TC) \quad (18)$$
$$\dot{V}Aexp_{normal} = Dp_{normal} + Dc_{normal} = 4.2 \quad (19)$$
$$0.29 * (39.78 - TP) + 1.78 * (47.27 - TC) = 4.2$$
$$(39.78 - TP) = (47.27 - TC) \quad (20)$$

Aside of calculating $[H^+csf]$, solving the CSF acid-base model at normal conditions provided a calculated value for normal CSF bicarbonate concentration (*$[HCO_3^-csf]$=26.4 mmol/l*). The importance of this value is to establish a reference value of $HCO3^-csf$ which could then be modified for

abnormal conditions of blood acid-base. This modification, $\Delta[HCO3^-]$, is calculated using equation 11 (figure 3-4) as the difference between normal values of bicarbonate concentration in CSF and mixed venous blood ($[HCO_{3,0}^-]$).

As mixed venous blood samples are seldom measured, the value of $[HCO_{3,0}^-]$ can be determined as follows. Assuming that there is equilibrium of BE between arterial and mixed venous blood, and steady state conditions, the total content of O_2 and CO_2 for mixed venous is calculated by subtracting $\dot{V}O_2$ from arterial blood, and adding $\dot{V}CO_2$ to arterial blood, respectively. Then, with values of total content of O_2 and CO_2 in mixed venous blood, and values of hemoglobin concentration, DPG and BE, the blood model (illustrated in figure 3-1) is solved to calculate $[HCO_{3,0}^-]$.

Following determination of the normal values of TC and TP, it is possible to simulate the effects of modifying the respiratory control model parameters (Sp, Sc, TP and TC) on $\dot{V}A$exp. The effect of modifying each model parameter on $\dot{V}A$exp is described in the following section, in order to identify the parameters of importance and select those which can be uniquely identifiable from clinical data. For that purpose, the set of models describing respiratory drive was used to perform simulations of $\dot{V}A$exp describing the effects of abnormal blood acid-base status, and increased $\dot{V}CO_2$.

4.2. SENSITIVITY ANALYSIS AND IDENTIFICATION

This section describes a sensitivity analysis of the respiratory control model parameters. To do so, factors that modify $\dot{V}A$exp are identified. Two groups of factors can modify $\dot{V}A$exp, i.e. those that are directly and indirectly measured, respectively. Directly measured factors are blood acid-base status and metabolism ($\dot{V}O_2$, and $\dot{V}CO_2$). Indirectly measured factors are e.g. respiratory control parameters or pulmonary gas-exchange parameters. The purpose of performing the sensitivity analysis is to determine the effects of variations in respiratory control parameters i.e. Sp, Sc, TP, and TC, on the simulated values of $\dot{V}A$exp, considering different conditions of directly measured factors (BE and $\dot{V}CO_2$). For simplicity, all sensitivity analysis simulations were performed assuming normal pulmonary gas-exchange parameters.

The sensitivity analysis of respiratory control model parameters is important for two reasons. First, if changes in parameter values produce similar changes in the simulated values of $\dot{V}A$exp then it might not be possible to uniquely identify these parameters, and choices may be required as to which

parameter values to fix and which to estimate. Second, if values of $\dot{V}Aexp$ vary very little with changes in parameter values, then it might not be important to estimate patient-specific values. To investigate the effects of variation in parameter values the respiratory control model was used to simulate $\dot{V}Aexp$ when varying parameter values under a wide range of physiological conditions including different blood acid-base status, and $\dot{V}CO_2$. Simulated values of $\dot{V}Aexp$ are plotted as the relationship between VT and fR, the product of which gives a constant minute ventilation $\dot{V}E$ (equation 14). By assuming a constant serial dead space (*Vds =150 ml*) in these simulations, plots of changes in $\dot{V}E$ and $\dot{V}Aexp$ are interchangeable. The relationship between VT and fR seen in plots illustrated in this section describe hypothetical response profiles of a patient ventilated in ACV, which responded adequately to changes in VT.

4.2.1. VARIATION IN BE AND $\dot{V}CO_2$ (DIRECTLY MEASURED FACTORS)

$\dot{V}E$ was simulated at three blood acid-base conditions i.e. normal (*BE=0 mmol/l*), metabolic acidosis (*BE=-4.2 mmol/l*), and metabolic alkalosis (*BE=5.3 mmol/l*), and at two $\dot{V}CO_2$ levels (*0.22* and *0.66 ml/min*) consistent with normal and elevated $\dot{V}CO_2$. Simulating these conditions was necessary as patients in support ventilation modes may present either blood acid-base abnormalities, increased $\dot{V}CO_2$ or both.

Figure 4-1 illustrates simulated $\dot{V}E$ at three blood acid-base conditions (normal, metabolic acidosis and alkalosis) and two levels of $\dot{V}CO_2$ for normal values of TP, TC, Sp and Sc as given in table 4-1. Simulated values of $\dot{V}E$ for each $\dot{V}CO_2$ level are illustrated in separate plots (figure 4-1 A and B). Figure 4-1 A illustrates the effects of metabolic acidosis and alkalosis at normal $\dot{V}CO_2$. Simulated $\dot{V}E$ is increased during metabolic acidosis and reduced during metabolic alkalosis. Figure 4-1 B illustrates the effects of metabolic acidosis and alkalosis at increased $\dot{V}CO_2$, showing that these factors act in combination, thus all $\dot{V}E$ curves are shifted towards increased ventilation. The set of models describing respiratory drive simulated increased $\dot{V}E$ in the following conditions: metabolic acidosis; and increase of $\dot{V}CO_2$. Conversely, simulated $\dot{V}E$ was reduced on metabolic alkalosis. These model simulations are in agreement with several experimental protocols, where metabolic alkalosis or acidosis was induced in subjects with dietary supplements. Subjects' $\dot{V}E$ was increased during metabolic acidosis, and was decreased during metabolic acidosis (11,12,103,104).

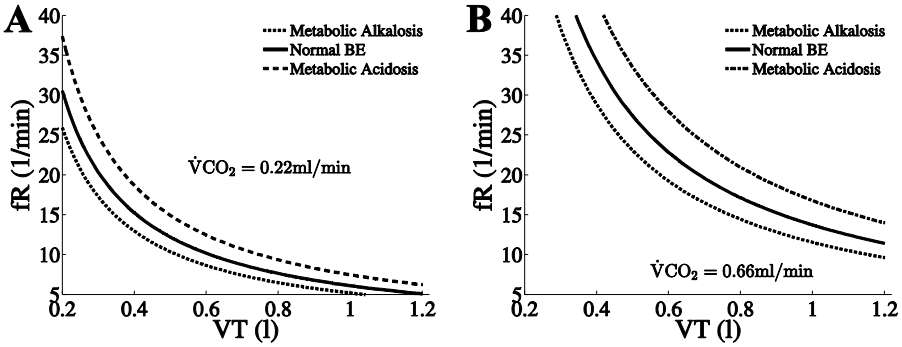

Figure 4-1. Simulations of $\dot{V}E$ at three different blood acid-base status at two levels of $\dot{V}CO_2$. $\dot{V}E$ is represented as the relationship between VT and fR, considering a constant Vds of 150 ml. Abnormal blood acid-base shifts $\dot{V}A$exp in respect to normal BE (solid lines). Metabolic acidosis (dashed lines) increases ventilation, and metabolic alkalosis (dotted lines) reduce ventilation. Increasing $\dot{V}CO_2$ increases $\dot{V}E$ (B), depending upon blood acid-base status.

4.2.2. VARIATION IN RESPIRATORY CONTROL MODEL PARAMETERS (INDIRECTLY MEASURED FACTORS)

The effects of varying respiratory control model parameters on $\dot{V}E$ can be simulated for different physiological conditions. Three different conditions described in the previous section were selected, those being: normal BE and normal $\dot{V}CO_2$; normal BE and increased $\dot{V}CO_2$; and metabolic acidosis and increased $\dot{V}CO_2$. The latter two represent abnormal conditions that increase $\dot{V}E$. Model parameters, TP, TC, Sp, and Sc, were varied one at a time, maintaining the others at normal values. Thresholds (TP and TC) represent the arterial blood and CSF $[H^+]$ concentration value, above which the respiratory drive increases linearly. These parameters were varied by subtracting and adding *5 nmol/l* to the corresponding normal values (*TP=37.75 nmol/l* and *TC=45.24 nmol/l*). Peripheral and central chemoreceptor sensitivities (Sp and Sc) are multiplicative parameters that determine the increase in ventilation due to arterial or CSF $[H^+]$ value above the respective threshold. Sensitivities were varied by multiplying the normal values (*Sp= 0.29 l/min/(nmol/l)* and *Sc=1.78 l/min/(nmol/l)*) by zero and 2.

Figure 4-2 illustrates simulated $\dot{V}E$ at different three physiological conditions, and different values of respiratory control model parameters. The plots in figure 4-2 are arranged in 3 columns and 4 rows. The plots on each column correspond to $\dot{V}E$ simulated under different physiological conditions: normal blood acid-base conditions and normal $\dot{V}CO_2$; normal blood acid-base conditions and increased $\dot{V}CO_2$; and metabolic acidosis and increased $\dot{V}CO_2$.

The plots on each row of figure 4-2 correspond to $\dot{V}E$ simulated under different physiological conditions with variations in a single respiratory control model parameter: Sc, TC, Sp and TP. The plots of simulated $\dot{V}E$ in the first row of figure 4-2, show that setting Sc to zero, reduces $\dot{V}E$ significantly. Increasing Sc, however, only slightly augments $\dot{V}E$. The plots of simulated $\dot{V}E$ in the second row of figure 4-2, show that reducing TC, augments the $\dot{V}E$, while increasing TC reduces the $\dot{V}E$. The shifts on simulated $\dot{V}E$ generated by modifying TC are almost symmetrical. The plots of simulated $\dot{V}E$ in the third and fourth rows of figure 4-2 show that modifying either Sp or TP generate marginal changes in model simulated $\dot{V}E$ in conditions of normal oxygenation. Variations in Sp and TP produced slight shifts on simulated $\dot{V}E$, hence, under conditions of normal oxygenation, Sp and TP do not change $\dot{V}E$ substantially and might not be the most important parameters for tuning patient response. In contrast, variations in Sc and TC produced similar, and significant shifts in simulated $\dot{V}E$ at the three conditions of blood acid-base status and $\dot{V}CO_2$. As the effects of Sc and TC are similar, estimating unique values of both from measurements of acid-base status and ventilation is not possible. It was therefore decided to fix the value of Sc at normal conditions and estimate TC for the specific patient. TC then represents the patient specific chemical drive. Selecting a central chemoreceptor parameter to describe the patient specific response is consistent with (110), where the respiratory control model showed that the central chemoreflex drive has a major role in the control of breathing, in the conditions of normal oxygenation.

4.3. TUNING THE RESPIRATORY DRIVE MODEL

In the previous section, TC was selected as the patient-specific model parameter describing respiratory control. The method to tune this model parameter to individual patients is presented in this section.

TC can be determined by solving equation 12 with clinically available data, such as: pHa, PaO_2, $PaCO_2$, VT, fR, $\dot{V}CO_2$, $FICO_2$ and $FECO_2$. For this purpose, all input and output variables from the respiratory control model are identified from the set of models illustrated in figure 3-4 E. The input variables are $[H^+a]$, PaO_2, and $[H^+csf]$, and the output variable is $\dot{V}Aexp$. The values of $[H^+a]$ and PaO_2 can be obtained from an arterial blood gas (ABG) analysis. $[H^+csf]$ can be calculated by solving equations 4-11, with $PaCO_2$ obtained from an ABG analysis, and $[HCO_{3,0}^-]$ estimated as described in section 4.1. The value of $\dot{V}Aexp$ can be calculated from the current patients' ventilation, using equation 14 and Vds calculated from equation 15. This implies that for tuning TC, patients are generating $\dot{V}Aexp$, and hence have an adequate

muscle function (*fM=1*). The value of TC can then be calculated by re-writing equation 12.

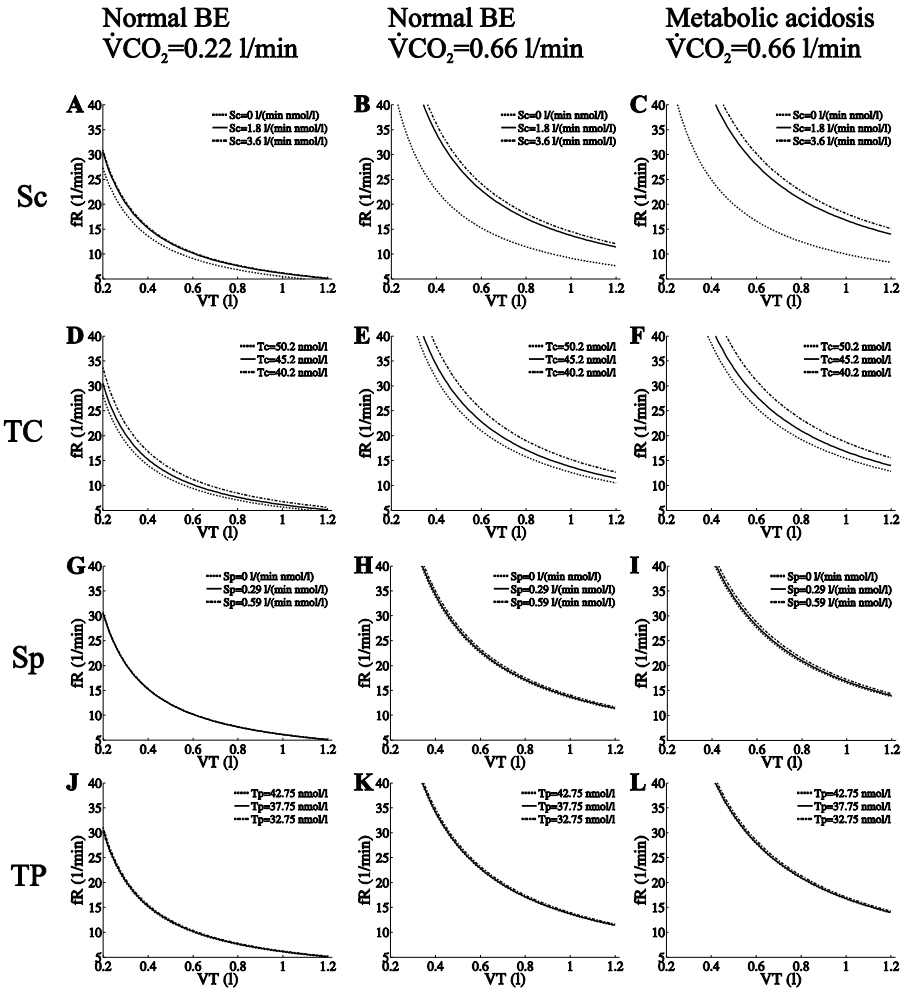

Figure 4-2. Simulations of V̇E with modifications in respiratory control model parameters, at three different conditions of blood acid-base and V̇CO₂. Each column corresponds to simulations of V̇E at: normal blood acid-base, and normal V̇CO₂; normal blood acid-base and V̇CO₂=0.66 ml/min; and metabolic acidosis and V̇CO₂=0.66 ml/min. Each row corresponds to simulations of V̇E on modifying a single respiratory control model parameter, i.e. Sc, TC, Sp and TC, respectively. The effects of modifying model parameters Sc and TC modify the respiratory response (plots A-C and D-F, respectively). In conditions of normal oxygenation, the effects of modifying model parameters Sp and TP do not modify the respiratory response (plots G-I and J-L).

$$TC = \frac{Dp+Dw-VE-(Vds*fR)}{Sc} + [H^+csf] \quad (21)$$

$$TC = \frac{\frac{2.373*([H^+a]-39.77)}{PaO_2-4}+2-VE-(Vds*fR)}{1.78} + [H^+csf]$$

Equation 21 can be solved assuming that Dw is known. For conscious spontaneously breathing patients in assisted ventilation Dw was set to 2 l/min, as mentioned in section 3.2.

To this point, the set of models describing respiratory response has been shown to describe typical respiratory responses due to abnormal blood acid-base status (metabolic acidosis or alkalosis), the patient-specific model parameter have been selected (i.e. TC), and a method for tuning such parameter to patient-specific conditions has been described. The set of models describing the respiratory response, therefore, needs to be evaluated with clinical data. The next section describes two clinical protocols designed to evaluate the set of models describing the respiratory drive.

4.4. CLINICAL PROTOCOLS

Chapter 3 described the set of models including respiratory control, and section 4.3 described a method to tune this model to patient-specific conditions. For this set of models to be useful in the clinical practice, the models need to be evaluated for their ability to describe patients' response to changes in the level of ventilator support. This section describes the clinical protocols performed to evaluate the set of models describing respiratory drive.

4.4.1. JUSTIFICATION OF THE CLINICAL PROTOCOLS

For the set of models presented here to be useful in clinical practice it is necessary that they can adequately describe the response of patients to changes in the level of ventilator support. Patient response to these changes can be measured using several variables. Response in ventilation can be measured from changes in VT or fR, and changes in blood acid-base status can be measured using continuous measurement of $FECO_2$, or by periodic arterial blood gas (ABG) analyses measuring pHa, or $PaCO_2$. The models can be used to simulate changes in these variables on varying the level of ventilator support. The principle of both protocols was therefore to compare

measured and model simulated values following changes in ventilation to see if the models could adequately describe patient response.

Two clinical protocols were performed with ventilator settings changes in two different ventilation modes, ACV and PSV. In both protocols the level of ventilator support (VT or PS) was changed on no more than 5 different occasions, each lasting 15 minutes to allow patients to reach steady state. Changes in VT or PS generate immediate changes in $\dot{V}E$. In turn, changes in $\dot{V}E$ alter alveolar fraction of gases, and consequently arterial blood gases (PaO_2 and $PaCO_2$). Changes in PaO_2 and $PaCO_2$, alter arterial blood and CSF $[H^+]$, modifying $\dot{V}Aexp$. At the end of each 15 minute period, steady state ventilation was expected and, values of fR, $FECO_2$, and pHa were measured, requiring data from the bedside patient monitor, and an ABG measurement. During the entire protocol, patients' indirect calorimetry, and pressure and flow measurements were used to measure VT, PS, $FECO_2$, $\dot{V}O_2$, and $\dot{V}CO_2$.

The two clinical protocols were needed to evaluate the set of models describing respiratory drive, this being necessary to describe patients' response to changes in VT or PS. Describing changes in VT requires less model complexity than describing changes in PS. Accordingly, in the first protocol, the set of models describing respiratory control was evaluated to describe patients' response to step changes in VT. For this reason, patients were ventilated in ACV, with the consequence that patients' response is limited to change fR to modulate ventilation. Patients' changes in fR were expected to resemble figures 4-1 and 4-2. Further protocol details are provided in section 4.4.2.

In the second protocol, the set of models describing respiratory drive was evaluated to describe patients' response to step changes in PS. For this reason patients were ventilated in PSV, and hence, patients were able to modulate ventilation by changing both fR and VT. During this protocol, Ceff was determined at each level of PS. Further protocol details are provided in section 4.4.2.

The set of models was used to simulate patients' response, to do so, models were tuned to individual patients' conditions at the beginning of the protocol (baseline conditions). Models simulated values of $FECO_2$, pHa, and fR, were calculated for each level of ventilator support, and compared against measured values. The statistical methods employed to quantify the difference between model simulated values and measured values of $FECO_2$, pHa and fR are described in section 4.4.3.

4.4.2. TECHNICAL DETAILS OF THE CLINICAL PROTOCOLS

This subsection describes the technical details of the clinical protocols as follows: general requirements for patient inclusion; procedure of clinical protocol performed in ACV; procedure of clinical protocol performed in PSV; and measurements taken during the protocol.

4.4.2.1 General requirements for patient inclusion

Data form the two clinical protocols were collected with ethical approval from the Ethics committee of Mid-Jutland, Denmark. The inclusion criteria for enrolling patients were: informed written and oral consent given by all patients or relatives, and in case of the latter, also the patient's general practitioner as required by Danish law; patients >18 years old; intubated and ventilated in support ventilation mode; dynamic lung compliance >30 ml/ cm H_2O at the time of inclusion; PEEP<10 cm H_2O; without hemodynamic instability (systolic blood pressure <90 mmHg with vasopressor); $PaCO_2$<8.5 kPa, and not being previously diagnosed with COPD; and presence of arterial catheter.

4.4.2.2 Clinical protocol performed with patients ventilated in ACV

After inclusion, ventilator mode was switched to V-C A-C (Evita XL, Dräger Medical, Lübeck, Germany). V-C A-C is a volume-controlled, time cycled, patient triggered ventilation mode i.e. ACV. The ventilator settings were selected as follows: flow trigger was set between 1-2 l/min, inspiratory flow at 30-35 l/min, inspiratory pause time at 0.1 sec, AutoFlow and automatic tube compensation (ATC) were disabled and the apnea setting (minimum fR) was set at 5/min. Baseline VT was adjusted to maintain $PaCO_2$ within 0.3kPa from original conditions. 15 minutes after the clinical protocol had started, ABG was measured (ABL Flex 800, Radiometer, Brønshøj, Denmark), and pulmonary gas-exchange was determined with a procedure involving 3-5 FIO_2 step changes (ALPE integrated, MermaidCare AP/S, Nr.Sundby, Denmark). Then, patients were subjected to a maximum of five VT-step changes of 50 ml each, beginning with reduction of VT from baseline.

After each 50 ml reduction, 15 minutes were waited to allow ventilation and CO_2 reach steady state followed by measurement of ABG. VT was further reduced only if pHa>7.3 and fR< 30/min or if the maximum 5-steps was not met. In case of completing the 5-step VT modifications solely with VT reduction, the protocol concluded with a measurement of ABG taken 15 minutes after resetting the ventilator the settings before the protocol started. Otherwise, VT was increased to the baseline level, and subsequently by 50 ml step increases. After each 50 ml increase, 15 minutes were waited to allow CO_2 to reach steady state, followed by measurement of ABG. VT was further

increased only if VT<8 ml/kg, and PIP< 30 cm H_2O, or the maximum of 5-step changes in VT was not met. After completing the five VT-step changes, or if not possible to further increase VT, the protocol concluded with a measurement of ABG taken 15 minutes after resetting the ventilator the settings before the protocol started.

4.4.2.3 Clinical protocol performed with patients ventilated in PSV

After inclusion, ventilator mode was shifted to P-C A-C (Evita XL, Dräger Medical, Lübeck, Germany). P-C A-C is a pressure-controlled, flow cycled patient triggered ventilation mode i.e. PSV. The ventilator settings were selected as follows: flow trigger was set to 5 l/min, slope (ramp time) was adjusted to achieve an inspiratory flow<60 l/min, apnea setting (minimum fR) was set to 5/min, and automatic tube compensation (ATC) was turned off. Baseline PS was adjusted to maintain $PaCO_2$ within 0.3kPa from original conditions. 15 minutes after the clinical protocol had started, ABG was measured (ABL Flex 800, Radiometer, Brønshøj, Denmark), and pulmonary gas-exchange was determined with a procedure involving 3-5 FIO_2 step changes (ALPE integrated, MermaidCare AP/S, Nr.Sundby, Denmark). Then, patients were subjected to a maximum of five PS-step changes of 2 cm H_2O each, beginning with reduction of PS from baseline.

After each PS reduction, 15 minutes were waited to allow ventilation and CO_2 reach steady state followed by measurement of ABG. PS was further reduced only if pHa>7.3 and fR<30/min, or if less than five PS-steps were performed and if PS>0 cmH_2O. In case of completing the five PS-step modifications solely with PS reduction, the protocol concluded with a measurement of ABG taken 15 minutes after resetting the ventilator the settings before the protocol started. Otherwise, PS was increased to the baseline level, and subsequently by 2 cmH_2O step increases. After each PS increase, 15 minutes were waited to allow steady state, followed by measurement of ABG. PS was further increased only if VT<8 ml/kg, and if PIP<30 cmH_2O, or if less than five PS-step changes were performed. After completing the five PS-step changes, or if it was not possible to further increase PS, the protocol concluded with a measurement of ABG taken 15 minutes after resetting the ventilator the settings before the protocol started.

4.4.2.4 Measurements taken during the protocol

To describe patients' response to changes in the level of ventilator support measurements of $FECO_2$, pHa and fR were required. Accordingly, pHa was obtained from an ABG measurement taken at the end of each step change of VT or PS (ABL Flex 800, Radiometer, Brønshøj, Denmark). Both fR and $FECO_2$ were obtained from patients' bedside monitor (CARESCAPE, GE

Healthcare, Helsinki, Finland). In order to calculate fR and $FECO_2$, and model input variables ($\dot{V}O_2$, $\dot{V}CO_2$, FIO_2, Vds, VT and PS), waveforms from measurements of airway pressure, flow, and concentration of O_2 and CO_2 were required. Each patient's waveforms were stored in a text file with the software S/5 Collect (GE-Healthcare, Helsinki, Finland). The data contained in the text files were used to determine breath by breath PS, FEO_2 and $FECO_2$; the flow waveform was integrated to determine VT, and used to calculate fR. A time window of one minute was used to calculate average values for fR, VT, $FECO_2$, $\dot{V}O_2$, $\dot{V}CO_2$, and for the second protocol effective compliance (Ceff).

Synchronizing data from the bedside monitor and ABG measurements taken during the protocol was performed with a case report form (CRF). The physician performing the clinical protocol was instructed to write-down in the CRF the time displayed in the bedside monitor at the time blood sampling. The time registrations on the CRF were used to synchronize ABG measurements and waveforms collected from the bedside monitor during the data analysis.

4.4.3. STATISTICAL ANALYSIS

This subsection describes the methods employed to compare model simulated and measured $FECO_2$, pHa and fR. The comparison between measured and simulated variables was performed with two methods: χ^2 test and Bland-Altman analysis. Summary statistics are reported as mean±SD if normally distributed, otherwise as median[range]. The association between patient variables was quantified with Pearson correlation coefficients (r-values).

4.4.3.1 χ^2 test

The difference between measured and model simulated values of fR, pHa and $FECO_2$ was quantified with a weighted residual sum of squares (WRSS) at each level of ventilator support. Equation 22 describes WRSS for 5 modifications in the level of ventilator support.

$$\mathrm{WRSS} = \sum_{n=5} \left(\frac{(fR_m - fR_s)^2}{{\sigma_{fR}}^2} + \frac{\left(FECO_{2_m} - FECO_{2_s}\right)^2}{{\sigma_{FECO_2}}^2} + \frac{(pHa_m - pHa_s)^2}{{\sigma_{pHa}}^2} \right)_n \tag{22}$$

where sub-indices *m* and *s* indicate measured or simulated values, and *n* indicates the number of modification in levels of ventilator support. The weights are the expected standard deviation of each variable (***σfR, σFECO$_2$,*** and ***σpHa***). The expected standard deviation of fR was assumed ***σfR=1/min***. The expected standard deviation of $FECO_2$ was assumed ***σFECO$_2$=0.25%***, which corresponds to the standard deviation of $FECO_2$ reported in healthy subjects (*0.2kPa*) (141), adjusted to humidity, temperature and measurement error from the device employed during the clinical protocol *(±0.02kPa*) (142). The expected standard deviation of pHa was assumed ***σpHa=0.015***, which corresponds to the effect produced by one standard deviation of $FECO_2$ in the calculation of pHa.

When the squared difference between measurements and model simulated values is equal to the squared expected standard deviation, the model fit is good. Thus, the expected value of the weighted residual sum of squares E(WRSS) for five VT levels is 15 as described in equation 23.

$$E(WRSS) = \sum_{n=5} \left(\frac{(fR_m - fR_s)^2}{{\sigma_{fR}}^2} + \frac{\left(FECO_{2_m} - FECO_{2_s}\right)^2}{{\sigma_{FECO_2}}^2} + \frac{(pHa_m - pHa_s)^2}{{\sigma_{pHa}}^2} \right)_n = 5 * 3 = 15 \quad (23)$$

A degree of freedom is lost for every estimated value of fM, because $FECO_2$ is used as part of model fit, and hence, its value is not part of model simulation. As an example, for a single value of fM (*q=1*), the E(WRSS) is 14 as described in equation 24.

$$E(WRSS) = \sum_{n=5} \left(\frac{(fR_m - fR_s)^2}{{\sigma_{fR}}^2} + \frac{\left(FECO_{2_m} - FECO_{2_s}\right)^2}{{\sigma_{FECO_2}}^2} + \frac{(pHa_m - pHa_s)^2}{{\sigma_{pHa}}^2} \right)_n - q = (5 * 3) - q = 14 \quad (24)$$

The goodness of model fit to data was performed with a χ^2 test that compares E(WRSS) with WRSS. To be conservative, a cut off value of p≥*0.2* was defined for interpreting a good model fit to measured data.

4.4.3.2 Bland-Altman analysis

The difference between measured and simulated values of fR, pHa and $FECO_2$ was quantified with Bland-Altman analysis for repeated measurements (143). Bias and limits of agreement between measured and model simulated variables were calculated for each variable.

4.5. CONCLUSION

This chapter has explored the behavior of the parameters of the respiratory control model, concluding that the model is complex enough to describe changes in ventilation with a single patient-specific parameter, i.e. TC. The method to estimate TC only requires clinically available data has been described. In principle, after tuning all model parameters (BE, DPG, fs, fA2, f2, SIDcsf, and TC) and using input variables ($\dot{V}O_2$, $\dot{V}CO_2$, Vds, VT or PS, fM, and Ceff), the set of models describing respiratory drive should be able to describe patient response to changes in ventilator support.

To be useful in clinical settings, the set of models needs to be evaluated for its ability to describe patients' response to changes in ventilator support as quantified by changes in $FECO_2$, pHa and fR. Two clinical protocols that produced changes in these variables have been designed to evaluate the set of models. In the first protocol, patients were ventilated in ACV, so that, VT was constant for each breath. In this way, patients' response was limited to changes in fR to modulate ventilation. In the second protocol, patients were ventilated in PSV, so that, PS was constant for each breath. In this way, patients were able to modify both fR and VT to modulate ventilation. Chapters 5 and 6 describe the results of each of the clinical protocols.

CHAPTER 5. EVALUATION OF THE SET OF MODELS IN ACV

The previous chapter described two clinical protocols for evaluating the set of models describing respiratory drive in patients being ventilated in ACV and PSV respectively. In addition, the tuning process of the respiratory control model parameter (TC) was also described. The objective of performing clinical protocols is to evaluate the set of models capability to describe patients' response to changes in ventilator support, to see whether they can predict patients' response to changes in ventilator support at the bedside.

This chapter presents the results from the evaluation of the set of models with the protocol of patients ventilated in ACV. Evaluation of the models in ACV provided a natural starting point, as VT delivered is not dependent on patient effort, meaning that patient response was confined to changes in fR. To assess whether the models formulated in this thesis are of an appropriate complexity to describe change in support, model simulated responses were calculated at three levels of model complexity, with these simulations compared to measurements from patients ventilated in ACV. Section 5.1 describes the justification of the use of ACV in this protocol. Section 5.2 presents patients' characteristics and model parameters. Section 5.3 shows model simulations at the three levels of model complexity. Section 5.4 presents the comparison of measured and model simulated variables (i.e. fR, pHa, and $FECO_2$). At the end of the chapter main findings of the clinical protocol are described.

5.1. JUSTIFICATION OF THE VENTILATION MODE

The set of models was evaluated in patients ventilated in V-C A-C ventilation mode, which is a specific ventilator brand name for ACV. This ventilation mode was selected for two practical reasons: a) VT is fixed, so patients' response to VT step changes was expected to resemble Figures 4-1 and 4-2; and b) the model complexity is reduced, because patient effort does not affect VT, and hence, the patient response is isolated to changes in fR (10,20,30,144). In this way, the protocol design allowed to determine the level of model-input complexity required to describe the respiratory control without the complications of patient effort, essentially isolating the chemical control component. The set of models describing respiratory drive were used to perform simulations of fR, pHa and $FECO_2$ considering different levels of model-input complexity.

Table 5-1. Demographics, diagnosis and model parameters.

Patient	**1**	**2**	**3**	**4**	**5**	**6**
Gender	M	F	F	F	F	M
Age (years)	56	56	84	84	77	64
Diagnosis	AP	PO	MI	ARDS	PO	PS
IBW (kg)	72	54	66	63	68	78
RASS	0	0	-4	-1	--	-1
Days on MV	11	31	4	14	4	8
fs (%)	0.0	16.0	3.0	15.0	13.0	13.0
High $\dot{V}/\dot{Q}$	3.98	26.0	9.27	5.19	4.77	4.47
Low $\dot{V}/\dot{Q}$	0.68	1.18	0.67	0.20	0.95	0.28
BE (mmol/l)	2.7	-1.0	2.0	3.8	4.0	1.5
Hb (mmol/l)	6.5	6.7	7.3	5.8	6.0	6.3
DPG (mmol/l)	5.0	4.5	5.0	6.0	2.7	2.9
SIDcsf (mmol/l)	33.2	30.1	33.1	35.9	35.7	34.1
TC (nmol/l)	41.4	44.4	38.5	50.8	40.2	47.8
Vds (l)	0.181	0.165	0.078	0.215	0.152	0.220
Lung mechanics during PSV						
PS (cmH_2O)	9.0	9.0	12.0	10.0	10.0	6.0
VT (l)	0.63	0.51	0.39	0.42	0.45	0.74
Compliance (l/cmH_2O)	0.07	0.06	0.03	0.04	0.04	0.12
Lung mechanics during ACV						
VT (l)	0.50	0.51	0.39	0.45	0.45	0.65
Flow (l/min)	30	30	30	30	35	35
Compliance (l/cmH_2O)	0.04	0.03	0.03	0.03	0.03	0.38
Resistance (cmH_2O /(l/min))	0.04	0.06	0.01	0.12	0.05	0.02

AP. Aspiration pneumonia; ARDS. Acute respiratory distress syndrome; EC. Endocarditis; MI. Myocardial infraction; PO. Postoperative complications; PS. Pneumonia and sepsis; RA. Retroperitoneal abscess; SA. Sarcoidosis.

Table 5-1. Demographics, diagnosis and model parameters (continuation).

Patient	**7**	**8**	**9**	**10**	**11**	**12**
Gender	F	M	F	F	M	M
Age (years)	65	78	79	74	39	74
Diagnosis	PS	MI	EC	PO	RA	SA
IBW (kg)	65	75	68	66	65	70
RASS	-2	-2	0	0	0	-3
Days on MV	3	3	--	19	15	1
fs (%)	6.0	7.0	11.0	5.0	1.0	7.0
High $\dot{V}/\dot{Q}$	25.2	8.64	21.2	4.45	1.43	1.89
Low $\dot{V}/\dot{Q}$	1.58	0.86	0.96	0.50	0.17	0.25
BE (mmol/l)	-0.6	3.4	-4.2	1.6	7.3	2.1
Hb (mmol/l)	5.7	5.6	5.4	5.4	4.8	6.6
DPG (mmol/l)	2.4	1.0	3.1	2.3	5.0	4.3
SIDcsf (mmol/l)	34.2	33.8	26.1	33.2	39.0	35.2
TC (nmol/l)	49.9	35.4	48.3	40.1	41.3	52.3
Vds (l)	0.100	0.192	0.217	0.135	0.152	0.222
Lung mechanics during PSV						
PS (cmH_2O)	12.0	9.0	12.0	12.0	6.0	12.0
VT (l)	0.41	0.52	0.50	0.32	0.45	0.57
Compliance (l/cmH_2O)	0.03	0.06	0.04	0.03	0.07	0.5
Lung mechanics during ACV						
VT (l)	0.45	0.52	0.50	0.36	0.45	0.57
Flow (l/min)	30	30	30	30	30	30
Compliance (l/cmH_2O)	0.03	0.03	0.03	0.02	0.05	0.04
Resistance (cmH_2O /(l/min))	0.09	0.10	0.03	0.01	0.05	0.13

AP. Aspiration pneumonia; ARDS. Acute respiratory distress syndrome; EC. Endocarditis; MI. Myocardial infraction; PO. Postoperative complications; PS. Pneumonia and sepsis; RA. Retroperitoneal abscess; SA. Sarcoidosis.

5.2. PATIENTS' CHARACTERISTICS AND MODEL PARAMETERS

Fifteen patients were enrolled in the clinical protocol, with three patients were not further considered for data analysis. Two of them did not complete the clinical protocol due to reduction in fR after the ventilator mode was changed to V-C A-C. The third patient was not included because data from the bedside monitor were lost due to computer failure. For the rest of the enrolled patients, basic demographics, diagnosis, and model parameters tuned at baseline are listed in Table 5-1. Patients presented different intensive care unit (ICU) admission diagnosis: three patients were mechanically ventilated due to post-operative complications (2, 5, 10); two patients presented myocardial infarction (3, 8); one patient presented retroperitoneal abscess (11); and the remaining patients were diagnosed with pneumonia, two recovering from sepsis (6, 7) and a single each with sarcoidosis (12), endocarditis (9), aspiration pneumonia (1), and recovering from acute respiratory distress syndrome (ARDS) (4).

Patients were age 74[39-84] years, had been 8[1-31] days on mechanical ventilation (at the time of the study), had Richmond Agitation-Sedation Scale (RASS) score -1[-4-0], and five were male. Model parameters were tuned at baseline conditions, these being: for pulmonary gas-exchange fs=7[0-16]%, fA2=0.45[0.09-0.98], and f2=0.85[0.53-0.98] (high $\dot{V}/\dot{Q}$ =5[1.4-26.0] and low $\dot{V}/\dot{Q}$ =0.7[0.2-1.6]); for blood acid-base BE=1.9±2.9 mmol/l, DPG=3.7±1.5 mmol/l, and Hb=6.0±0.7 mmol/l; for chemoreflex respiratory drive SIDcsf=33.6±3.18 mmol/l, and TC=44.2±5.48 nmol/l; and for ventilation Vds=0.17±0.05 l. Blood acid-base abnormalities at baseline explain the variation of SIDcsf (see table 5-1). For instance, patient 9 presented the lowest BE and SIDcsf, and patient 11 presented the highest BE and SIDcsf at baseline conditions.

5.3. MODEL SIMULATIONS WITH DIFFERENT LEVELS OF MODEL COMPLEXITY

The patients included in the protocol were subjected up to five different levels of VT. During that period of time, the input variables ($\dot{V}O_2$, $\dot{V}CO_2$, and Vds) of the set of models were continuously measured. To determine the required level of model complexity to adequately describe patients' response, the set of models was used to simulate fR, pHa and $FECO_2$, considering three levels of model-input complexity. For level 1, $\dot{V}CO_2$ and Vds were considered constant, with their respective value equal baseline conditions. Muscle function (fM) was assumed adequate, and considered constant and equal to 1 at each VT level. For level 2, $\dot{V}CO_2$ and Vds were measured at each VT

step, and fM was assumed adequate, and considered constant and equal to 1 at each VT level. For level 3, $\dot{V}CO_2$ and Vds were measured at each VT step, and fM was estimated at each VT level. Three simulated values of fR, pHa and $FECO_2$, corresponding to each level were performed.

Figures 5-1 and 5-2 (patients 1, 2 respectively) illustrate two contrasting examples of patient-response to changes in VT. Patient 1 (figure 5-1) is a representative case. Patient 2 (figure 5-2) is an extreme case that required the lowest values of fM (fM≈0.7) among the patient group. Blank symbols represent measured values, and grey symbols represent model simulated values. Error bars represent one SD of continuously measured variables over the last minute of ventilation at each VT level. Each figure is divided into 4 rows (A-D). The first 3 rows (A-C) illustrate measurements and model simulated values for the three levels of model complexity, with row A illustrating simulations performed assuming constant $\dot{V}CO2$, Vds and fM=1 (level 1), row B accounting for changes in $\dot{V}CO_2$, and Vds, and assuming adequate muscle function (fM=1), and row C accounting for changes in VD, $\dot{V}CO_2$ and fM. Row D illustrates values of $\dot{V}CO_2$, Vds and fM at each VT level. The appendix A, includes plots in rows C and D of figures 5-1 and 5-2 for all twelve patients.

Patients 1 and 2 responded with increasing fR on reduction in VT. Nine of the twelve patients responded similarly, with the remaining three (3, 7, 12) showing little change in fR on changing VT (see appendix A). Patient 1 presented little change in pHa or $FECO_2$ with decreasing VT in contrast, patient 2 presented large changes in pHa and $FECO_2$ at the lowest VT. Patient 1 showed systematic decrease in VD and increase in $\dot{V}CO_2$ on reduction of VT (figure 5-1 D1-D2). A similar pattern was seen in six patients (1, 5, 6, 8, 9, 10), the remaining patients showed no systematic changes. Model simulations corresponding to level 1 of model-input complexity for patients 1 and 2 (figures 5-1 and 5-2, row A) resulted in simulated values of $FECO_2$, fR, and pHa (grey symbols) different from measurements (blank symbols).

Figures 5-1 and 5-2 show that there is an improvement in model fitting as the model inputs increase. The next section describes statistics reporting the goodness of fit of the three levels model-input assumption, and presents Bland-Altman analysis for the differences between measured and model simulated values of fR, pHa and $FECO_2$.

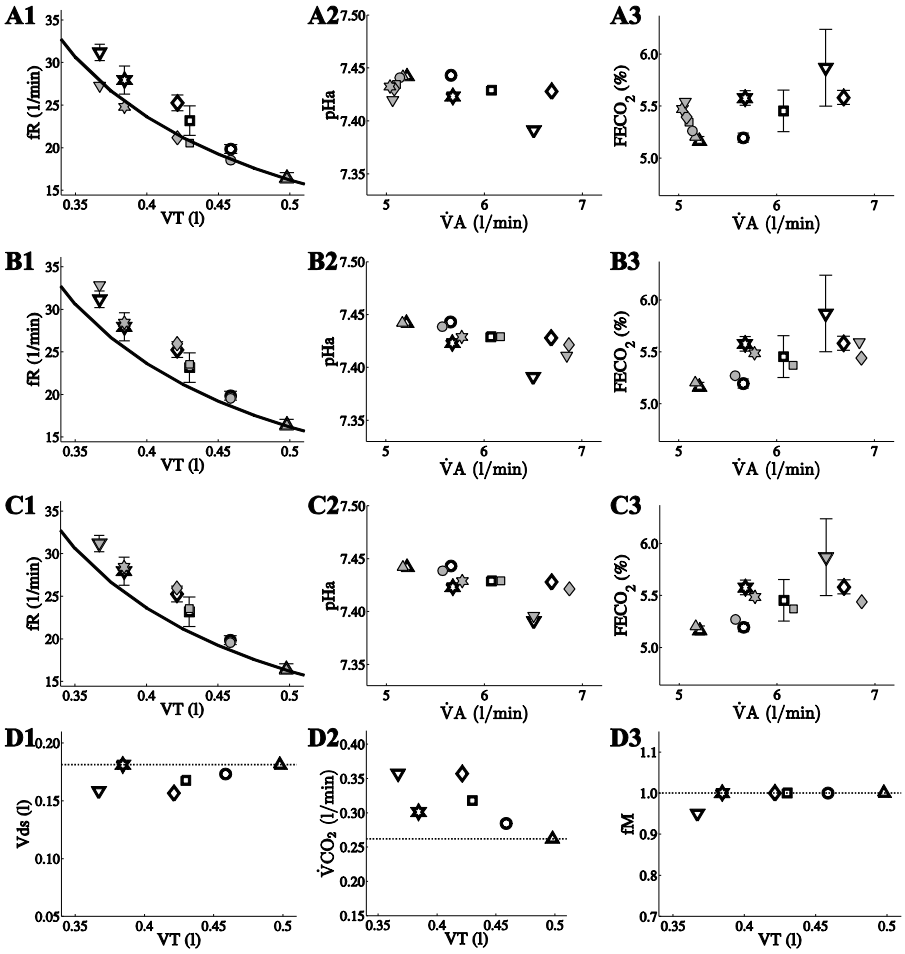

Figure 5-1. Measured and model simulated values of fR, pHa, and $FECO_2$ for a typical patient response to changes in VT. Blank symbols represent measured values, and grey symbols represent model simulated values. Rows A-C illustrate model simulations of fR (column 1), pHa (column 2), and $FECO_2$ (column 3), using different level of model complexity. Row D illustrates the input variables required for each level of model complexity. Row A corresponds to complexity including constant Vds, $\dot{V}CO_2$ and fM (dotted lines in D1-3). Row B corresponds to complexity including variable Vds, and $\dot{V}CO_2$ (symbols in D1-2), and fM=1 (dotted line in D3). Row C corresponds to complexity including variable Vds, $\dot{V}CO_2$ and fM (symbols in D1-3). The solid line in plots A1, B1 and C1, represents $\dot{V}E$ calculated at baseline conditions (upwards triangle), considering constant values of Vds and $\dot{V}CO_2$ are represented with dotted lines in the plots D1-2. Each symbol corresponds to a different VT level: first (circles), second (squares), third (diamonds), fourth (hexagrams) and fifth (downward triangles) VT modification, and baseline (upward triangles).

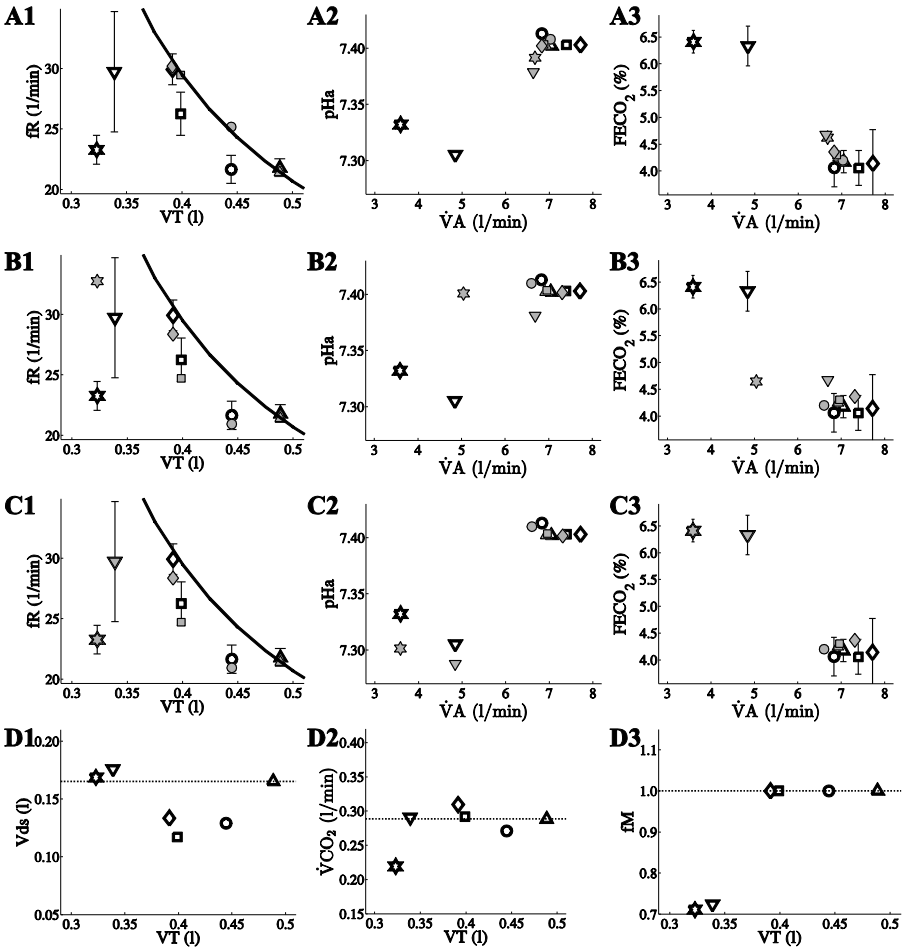

Figure 5-2. Measured and model simulated values of fR, pHa, and $FECO_2$ for patient response to changes in VT, where fM was significantly low. Blank symbols represent measured values, and grey symbols represent model simulated values. Rows A-C illustrate model simulations of fR (column 1), pHa (column 2), and $FECO_2$ (column 3), using different level of model complexity. Row D illustrates the input variables required for each level of model complexity. Row A corresponds to complexity including constant Vds, $\dot{V}CO_2$ and fM (dotted lines in D1-3). Row B corresponds to complexity including variable Vds, and $\dot{V}CO_2$ (symbols in D1-2), and fM=1 (dotted line in D3). Row C corresponds to complexity including variable Vds, $\dot{V}CO_2$ and fM (symbols in D1-3). The solid line in plots A1, B1 and C1, represents $\dot{V}E$ calculated at baseline conditions (upwards triangle), considering constant values of Vds and $\dot{V}CO_2$ are represented with dotted lines in the plots D1-2. *Each symbol corresponds to a different VT level: first (circles), second (squares), third (diamonds), fourth (hexagrams) and fifth (downward triangles) VT modification, and baseline (upward triangles).*

5.4. COMPARISON BETWEEN MEASURED AND MODEL SIMULATED DATA

The analysis of the appropriate level of model complexity to describe patients' response is shown in table 5.2. This table reports the goodness of fit for the three levels of model-input complexity at each level of VT (rows) and for each

Table 5-2. Values of WRSS between measured data and model simulations for the three analyses; and F-test for comparison between the analyses.

Patient	1	2	3	4	5	6
	Level of model complexity: 1					
High VT	1.5	10.6	16.0	8.0	0.5	8.5
	6.1	9.4	6.7	1.5	1.0	15.2
	14.5	0.8	35.5	1.0	0.9	4.3
	8.8	367.7	*	58.6	1.0	8.4
Low VT	18.1	127.6	*	*	8.3	137.9
$\sum$(WRSS) χ^2	49.1	516.1	58.2	69.1	11.7	174.4
test p	0.0	0.0	0.0	0.0	0.70	0.0
	Level of model complexity: 2					
High VT	0.3	0.8	0.5	6.2	0.6	0.2
	0.2	2.9	2.5	0.9	1.3	2.5
	0.9	2.8	45.2	1.2	0.9	0.8
	0.5	144.8	*	9.5	0.1	6.7
Low VT	5.2	175.4	*	*	5.7	34.1
$\sum$(WRSS) χ^2	7.0	326.8	48.2	17.7	8.6	44.2
test p	0.95	0.0	0.0	0.12	0.90	0.0
	Level of model complexity: 3					
High VT	0.3	0.8	0.5	2.2†	0.6	0.2
	0.2	2.9	2.5	0.9	1.3	0.3†
	0.9	2.8	0.4†	1.2	0.9	0.8
	0.5	4.2†	*	1.4†	0.1	6.7
Low VT	0.1†	1.4†	*	*	0.4†	0.6†
$\sum$(WRSS) χ^2	1.97	12.1	3.4	5.7	3.4	8.5
test p	0.99	0.52	0.91	0.84	0.99	0.81

* Missing VT step changes due to patient outside protocol defined ranges.
† WRSS value calculated including estimation of fM.
‡ Comparison of goodness of fit between analyses 1 and 2.
§ Comparison of goodness of fit between analyses 2 and 3.

patient (columns). For level 1, χ^2 p-values showed poor model fit to data in all patients except patient 5. For level 2, χ^2 p-values showed poor model fit to data except in four patients (1, 5, 8, 10), where χ^2 p-value≥0.2. In six of the patients (2, 3, 4, 6, 7, 12), poor model fit to data was due to patients having inadequate $\dot{V}A$ to maintain pHa and $FECO_2$ at the lowest VT settings. An F-ratio test showed the model fit of analysis 2 was significantly better than

Table 5-2. Values of WRSS between measured data and model simulations for the three analyses; and F-test for comparison between the analyses (continuation).

							F-Test
Patient	7	8	9	10	11	12	
	Level of model complexity: 1						
High VT	8.1	24.0	47.7	27.6	70.4	31.3	
	4.0	1.3	71.8	38.6	64.6	28.3	
	21.3	15.0	2.0	6.6	64.9	12.6	
	*	8.0	8.6	30.9	4.0	*	
Low VT	*	*	*	*	*	*	
∑(WRSS) χ^2 test p	33.5 0.0	48.3 0.0	130.1 0.0	103.7 0.0	203.9 0.0	72.2 0.0	
							p<0.001‡
	Level of model complexity: 2						
High VT	0.6	5.3	5.5	2.0	55.0	1.0	
	0.0	1.4	21.7	1.4	7.8	0.9	
	16.9	4.8	1.6	0.3	9.9	17.4	
	*	4.3	2.8	0.2	6.5	*	
Low VT	*	*	*	*	*	*	
∑(WRSS) χ^2 test p	17.5 0.04	15.7 0.20	31.7 0.0	3.9 0.99	79.2 0.0	19.4 0.02	
							p<0.001§
	Level of model complexity: 3						
High VT	0.6	0.3†	5.5	2.0	2.8†	1.0	
	0.0	1.4	0.3†	1.4	1.1†	0.9	
	0.6†	1.8†	1.6	0.3	2.8†	0.0†	
	*	4.3	2.8	0.2	1.0†	*	
Low VT	*	*	*	*	*	*	
∑(WRSS) χ^2 test p	7.8 0.65	10.3 0.5	3.9 0.99	7.65 0.47	1.97 0.98	7.8 0.65	

* Missing VT step changes due to patient outside protocol defined ranges.
† WRSS value calculated including estimation of fM.
‡ Comparison of goodness of fit between analyses 1 and 2.
§ Comparison of goodness of fit between analyses 2 and 3.

analysis 1 ($p<0.001$). For level 3, χ^2 p-values showed good model fit to data ($p>0.2$) in all patients. An F-ratio test showed the model fit of analysis 3 was significantly better than analysis 2 ($p<0.001$). According to table 5-2, the model complexity requiring variable $\dot{V}CO_2$, and Vds, and muscle function (fM), provides the best fit to data.

In addition to the χ^2 test, a Bland-Altman analysis was performed to compare measured and model simulated fR, pHa and $FECO_2$ for the most complex of the three models evaluated, i.e. that presented in this thesis, as illustrated in Figure 5-3. The bias ± limits of agreement for each variable were: fR 0.0±1.4 1/min (figure 5-3 A); pHa 0.003±0.020 (figure 5-3 B); and $FECO_2$ 0.000±0.003 (figure 5-3 C). Low bias and narrow limits of agreement indicate adequate model description of patients' response. The bias and limits of agreement for pHa are comparable to values estimated in a study designed to calculate blood variables, after exposure of blood samples to specific concentrations of O_2 and CO_2 (38).

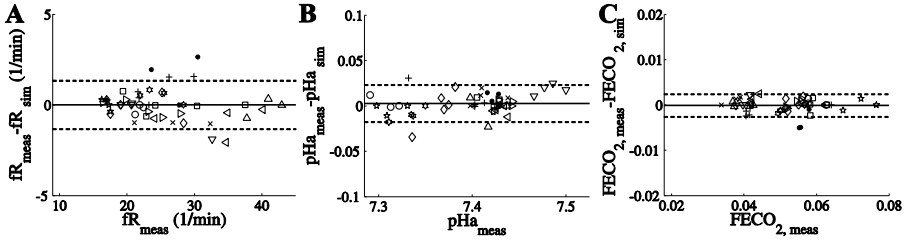

Figure 5-3. Bland-Altman plots of difference between measured and simulated patient response to changes in VT. Each symbol illustrates a single patient i.e. right-pointing triangle (patient 1), vertical cross (patient 2), upwards triangle (patient 3), hexagram (patient 4), square (patient 5), diamond (patient 6), circle (patient 7), downwards triangle (patient 8), diagonal cross (patient 9), left-pointing triangle (patient 10), dot (patient 11) and pentagram (patient 12). The solid lines illustrate the bias between measured and simulated values, and the dashed lines illustrate the limits of agreement. Each plot illustrates differences between measured and simulated fR (A), pHa (B) and $FeCO_2$ (C).

5.5. CONCLUSION

This chapter presented the evaluation of the set of models describing respiratory drive performed with a clinical protocol in which patients were ventilated in ACV. The major finding of this study was that the set of models taking into account changes in $\dot{V}CO_2$, Vds, and representation of muscle function (fM) i.e. the most complex of the three models evaluated, provided a good description of measured values of $FECO_2$, fR, and pHa in all patients.

The set of models was shown to adequately describe 12 patients' response in terms of blood acid-base status (pHa), pulmonary gas-exchange ($FECO_2$) and respiratory control (fR) to changes in VT. In addition, the set of models was shown to be tunable for individual patients, and seems to describe the clinical observation that patients have a preferred level pHa and $FECO_2$ during modification of ventilator support (41,42), unless respiratory distress or over-distention result from modifying the level of ventilator support (18,21).

The set of models describing respiratory drive seems to predict patient response to changes in VT adequately, however, patients in assisted ventilation are typically ventilated in other ventilator modes than ACV. The vast majority of the patients ventilated in assisted ventilation are in PSV (9). This ventilation mode provides a constant PS during inspiration instead of delivery of a fixed VT, thus, patients are capable of modulating both VT and fR. Accordingly, PSV increases the level of model complexity, and requires the quantification of changes in patient effort if the correct relationship between the level of pressure support and the tidal volume is to be represented. The next chapter describes the evaluation of the set of models describing the respiratory drive model in PSV.

CHAPTER 6. EVALUATION OF THE SET OF MODELS IN PSV

In chapter 4 two clinical protocols were described for evaluating the set of models describing respiratory drive in patients being ventilated in ACV and PSV respectively. The objective of performing these protocols is to evaluate the set of models capability to describe patients' response to changes in ventilator support, and thus, its ability to describe patients' response to changes in ventilator support at the bedside. The previous chapter described the evaluation of the set of models in ACV. In addition to evaluating the set of models, the correct level of model complexity required to describe patients' response to changes in ventilator support was evaluated. This chapter presents the results from the evaluation of the set of models with a protocol in which patients were ventilated in PSV. This protocol was designed to evaluate the respiratory response taking into account changes in patient effort. Section 6.1 describes the justification of the ventilation mode. Section 6.2 presents patients' characteristics and model parameters. Section 6.3 presents the comparison between measured and model simulated fR, pHa, and $FECO_2$, with model simulations including changes in effective compliance (Ceff). At the end of the chapter main findings of the clinical protocol are described.

6.1. JUSTIFICATION OF THE VENTILATION MODE

The set of models was evaluated in patients ventilated in P-C A-C ventilation mode, which is a specific ventilator brand name for PSV. This ventilation mode was selected for two practical reasons: a) PS is fixed, so patients' respiratory response to PS step changes has two components VT and fR; and b) the delivery of inspiratory flow is flow-cycled, so that, VT depends upon patient effort (9,17). It is also a commonly used mode, meaning that evaluation of the models in this mode is important for their clinical applicability.

6.2. PATIENTS' CHARACTERISTICS AND MODEL PARAMETERS

Fifteen patients were enrolled in the clinical protocol, with three patients not considered for data analysis. One patient developed apnea before performing modifications in PS, a second patient died after consent was approved and before the protocol started, and a third patient presented an erratic breathing

Table 6-1. Demographics, diagnosis, and model parameters.

Patient	**1**	**2**	**3**	**4**	**5**	**6**
Gender	M	M	M	M	M	M
Age (years)	76	69	66	78	70	76
Diagnosis	POS	ALI	AP	Renal CA	SAP	PS
IBW (kg)	84	60	64	80	82	70
RASS	-3	0	0	-2	-3	-3
Days on MV	12	1	16	2	17	6
fs (%)	7	0	20	7	6	8
High $\dot{V}/\dot{Q}$	3.0	3.8	92.9	2.5	6.6	43.6
Low $\dot{V}/\dot{Q}$	0.4	0.2	1.1	0.4	1.0	1.08
BE (mmol/l)	-0.8	7.2	-2.2	3	-2.9	-0.1
Hb (mmol/l)	5.2	5.9	7.6	5.4	5.7	6.4
DPG (mmol/l)	3.2	1.2	4.4	3.2	3.6	2.7
SIDcsf (mmol/l)	29.9	37.3	27.3	34.3	29.1	32.0
TC (nmol/l)	44.7	41.7	37.7	45.2	53.8	49.7
Vds (ml)	244	269	387	356	139	365
Lung mechanics						
PS (cmH_2O)	8	12	16	14	13	12
VT (ml)	620	440	630	790	360	950
Ceff (l/cmH_2O)	0.08	0.04	0.04	0.06	0.03	0.08
PEEP (cmH_2O)	9	7	9	7	7	6

POS. Postoperative sepsis, ALI. Acute lung injury; AP. Aspiration pneumonia; SAP. severe acute pancreatitis; PS Pneumonia and sepsis; HA. Heart attack

pattern, making it impossible to integrate flow waveform to calculate VT. For the rest of the enrolled patients, basic demographics, diagnosis, and model parameters tuned at baseline are listed in table 6-1. Patients presented different intensive care unit (ICU) admission diagnosis: two patients presented heat attack (8, 9), two patients presented aspiration pneumonia (3, 11), two patients presented acute lung injury (2, 10); thee patients presented pneumonia and sepsis (6, 7, 12); and a single each presented post-operative complications (1); renal cancer (4); and severe acute pancreatitis (5).

Patients were age 72.5[55-80] years, had been 9[1-30] days on mechanical ventilation (at the time of the study), had RASS score -2[-4-0], and four were female. Model parameters were determined at baseline conditions, these being: for pulmonary gas-exchange fs= 8[0-20]%, fA2= 0.44[0.12-0.78], and f2= 0.9[0.59-0.99] (high $\dot{V}/\dot{Q}$ = 11.4[2.5-83] and low $\dot{V}/\dot{Q}$ = 0.7[0.2-1.7]); for blood acid-base BE=3.3±4.9 mmol/l, DPG= 4.25±2.13 mmol/l, and Hb=5.93

Table 6-1. Demographics, diagnosis, and model parameters (continuation).

Patient	**7**	**8**	**9**	**10**	**11**	**12**
Gender	F	F	F	M	M	F
Age (years)	55	80	79	72	67	73
Diagnosis	PS	HA	HA	ALI	AP	PS
IBW (kg)	65	68	60	60	80	58
RASS	-1	-4	-3	0	-1	0
Days on MV	4	5	9	20	--	30
fs (%)	18	16	16	0	10	13
High $\dot{V}/\dot{Q}$	70.5	4.5	2.9	16.3	16.1	41.8
Low $\dot{V}/\dot{Q}$	1.7	0.4	0.4	0.3	0.9	1.5
BE (mmol/l)	0.1	4.3	8.4	12.4	8.6	1.6
Hb (mmol/l)	5.2	7.5	5.7	6.7	4.6	5.3
DPG (mmol/l)	3.4	4.9	4.7	10.2	4.8	4.2
SIDcsf (mmol/l)	31.5	36.5	40.3	43.9	39.5	30.8
TC (nmol/l)	40.3	34.9	37.0	44.4	35.1	36.0
Vds (ml)	189	217	114	185	217	180
Lung mechanics						
PS (cmH_2O)	9	7	10	14	10	14
VT (ml)	640	450	390	240	380	400
Ceff (l/cmH_2O)	0.07	0.06	0.04	0.02	0.04	0.03
PEEP (cmH_2O)	9	7	6	5	8	6

POS. Postoperative sepsis, ALI. Acute lung injury; AP. Aspiration pneumonia; SAP. severe acute pancreatitis; PS Pneumonia and sepsis; HA. Heart attack

±0.94 mmol/l; for chemoreflex respiratory drive SIDcsf=34±5 mmol/l, and TC=42.1±5.9 nmol/l; and for ventilation Vds=0.26±0.13 l. Blood acid-base abnormalities at baseline explain variation of SIDcsf (see table 6-1). For instance patient 5 presented the lowest BE and low SIDcsf, and patient 10 presented the highest BE and SIDcsf.

Patients' responses on modifying the level of PS are illustrated in figures 6-1 and 6-2. Figures 6-1 illustrates measured and calculated data describing respiratory stress for all patients at all PS levels. Figures 6-1 A-B illustrate the ventilatory response i.e. fR and VT at each PS level. The r-values for the correlation between PS and ventilatory response were r=0.45 ($p<0.001$) for fR, and r=-0.12 (p=0.35) for VT. Both r-values indicate large variations across the patient group. In some patient's, e.g. patient 6 (diamonds), fR increased

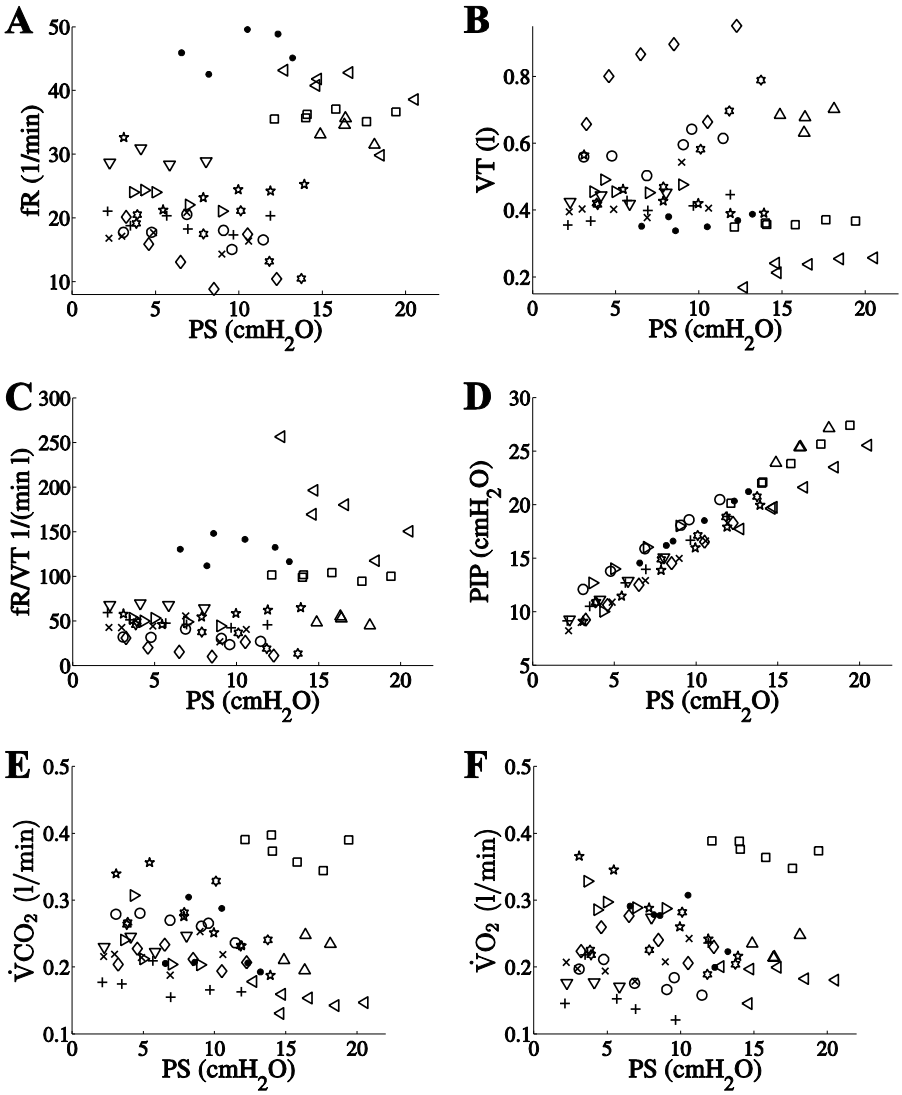

Figure 6-1. Data describing spontaneously breathing patients ventilated at different PS levels. Each symbol illustrates a single patient i.e. right-pointing triangle (patient 1), vertical cross (patient 2), upwards triangle (patient 3), hexagram (patient 4), square (patient 5), diamond (patient 6), circle (patient 7), downwards triangle (patient 8), diagonal cross (patient 9), left-pointing triangle (patient 10), dot (patient 11) and pentagram (patient 12). Patients' responses to different PS levels are illustrated in terms of fR (A), Vt (B), fR/Vt (C), PIP (D), $\dot{V}CO_2$ (E), and $\dot{V}O_2$ (F).

and VT decreased on reducing PS, while in others e.g. patient 5 (squares), fR and VT remained relatively constant. Figures 6-1 C-D illustrate surrogate measures for respiratory stress, i.e. the fR/VT ratio, and positive inspiratory pressure (PIP) for all PS levels. The r-value for the correlation between PS and fR/VT was r=0.43 ($p<0.001$), indicating a wide range of fR/VT variation across the patient group. In some cases, this ratio increased at lower values of PS, e.g. patient 10 (left-pointing triangle) indicating increased respiratory stress. The r-value for the correlation between PS and PIP was r=0.97 ($p<0.001$), indicating linear increase of PIP with PS. Figures 6-1 E-F illustrate metabolism ($\dot{V}CO_2$ and $\dot{V}O_2$) for all patients at all PS levels. The r-values for the correlation between PS and metabolism were r=0.01 (p=0.96) for $\dot{V}CO_2$ and r=0.13 (p=0.30) for $\dot{V}O_2$, indicating a large variation of metabolism with PS. The respiratory exchange ratio (RER) for the patient population at all PS levels was 1.03±0.22.

Figure 6-2 illustrates the acid-base status for all patients at the calculated alveolar ventilation from measured data ($\dot{V}$Apat) associated with all PS levels. A wide range of $FeCO_2$, $PaCO_2$, and pHa levels were seen across the group. A tendency for higher $FeCO_2$ and $PaCO_2$ levels was observed at lower VApat across the patient group. The r-value for the correlation between VApat and $FeCO_2$ was r=-0.72 ($p<0.001$) and between $\dot{V}$Apat and $PaCO_2$ was r=-0.78 ($p<0.001$).

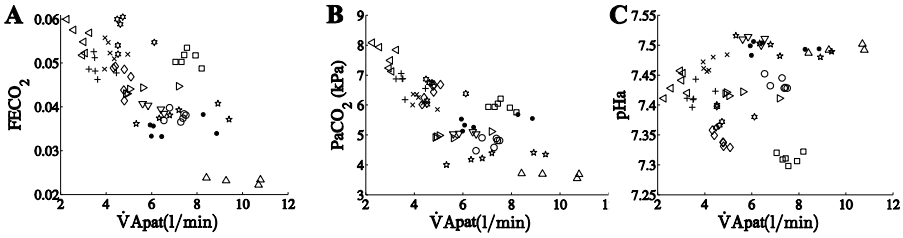

Figure 6-2. Measured variables describing blood acid-base status plotted against estimated alveolar ventilation ($\dot{V}$Apat) during changes in PS. Each symbol illustrates a single patient i.e. right-pointing triangle (patient 1), vertical cross (patient 2), upwards triangle (patient 3), hexagram (patient 4), square (patient 5), diamond (patient 6), circle (patient 7), downwards triangle (patient 8), diagonal cross (patient 9), left-pointing triangle (patient 10), dot (patient 11) and pentagram (patient 12).

Two contrasting patients are presented as examples describing the relationship between ventilation and blood acid-base status. Patient 5 (squares in figures 6-1 and 6-2) presented the lowest pHa, highest $\dot{V}CO_2$, and lowest BE (table 6-1), in contrast, patient 3 (upwards triangles in figures 6-1

and 6-2) presented the lowest $FECO_2$, high values of pHa, and the largest high $\dot{V}/\dot{Q}$ ratio (table 6-1). The set of models describing the respiratory drive was used to describe these rather complex patients' responses. The next section presents the evaluation of the respiratory drive simulated variables against measured data.

6.3. COMPARISON BETWEEN MEASURED AND SIMULATED VARIABLES

The patients included in the protocol were subjected up to five different levels of PS. During that period of time, the input variables ($\dot{V}O_2$, $\dot{V}CO_2$, Vds, and VT) of the set of models were continuously measured, as these data were necessary to determine patients' response. All model parameters estimated at baseline conditions are given in table 6-1. In addition, figure 6-3 provides values of those model parameters estimated at different PS levels, i.e. Vds, Ceff, and fM, which are necessary to simulate patients' response to changes in PS with the set of models describing the respiratory drive. Vds showed no obvious patterns on modifying PS (figure 6-3 A). Patients 3 (upwards triangles), 4 (hexagram), and 6 (diamonds) presented high values of Vds.

Ceff changed in almost all patients as PS was modified (figure 6-4 B). Patients 1, 3 and 5 (left-pointing triangle, upwards triangle and square) showed a relatively constant Ceff on reduction of PS, in contrast, the rest of the patients increased Ceff, presumably by increasing patient effort. The shape of figure 6-4 B is in agreement with the clinical observation that increasing PS reduces patient effort (41,42,138,145), and conversely, reducing PS increases patient effort. Two additional characteristics of the PS-Ceff plot are interesting: the points appear to lie on a single curve that can describe the relationship between PS and patient effort; and at high levels of PS, Ceff is comparable with compliance measured in sedated patients (58).

Muscle function (fM) was equal to 1 in almost all patients on modifying PS (figure 6-3 C). Patients 2 (vertical crosses), 4 (hexagrams), and 12 (pentagram) presented reduction in $\dot{V}$Apat (fM<1) on reducing PS. Conversely, patients 5 (squares), and 10 (left-pointing triangles) presented an increase in VApat (fM>1) on PS>10 cm H_2O.

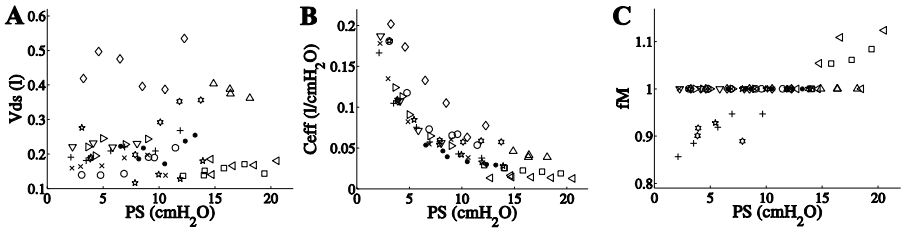

Figure 6-3. Model inputs estimated at each PS level. Serial dead space (Vds) (A), effective compliance (Ceff) (B), and muscle function (fM) (C). Each symbol illustrates a single patient i.e. right-pointing triangle (patient 1), vertical cross (patient 2), upwards triangle (patient 3), hexagram (patient 4), square (patient 5), diamond (patient 6), circle (patient 7), downwards triangle (patient 8), diagonal cross (patient 9), left-pointing triangle (patient 10), dot (patient 11) and pentagram (patient 12).

A χ^2 test was performed to determine the goodness of fit of the model simulations to measured data. Statistics reporting the goodness of fit at each level of PS (rows) and for each patient (columns) are given in table 6-2. The χ^2 p-values showed good model fit to data (p>0.2) in all patients but patients 6 and 11. Bland-Altman plots were used to compare the values of measured and simulated values for the group as a whole and for these two patients in detail. Figure 6-4 illustrates these Bland-Altman analyses for the three measured and simulated variables (fR, pHa and $FECO_2$). Bias and limits of agreement for each variable were: fR 0.7±2.2 1/min (figure 6-4 A); pHa -0.0007±0.019 (figure 6-4 B); and $FECO_2$ 0.001±0.003 (figure 6-4 C). The bias and limits of agreement for pHa and $FECO_2$ are comparable to those estimated in the previous chapter. Patient 11, illustrated with dots, presented the worst simulation of fR. Patient 11 presented high fR (45.7±4.5 1/min), thus the differences represent a relatively small percentage of the measured fR in this patient.

Patient 6, illustrated with diamonds in figures 6-4 B-C, presented with the highest values of Vds amongst the patient group, and on reduction of PS (from 12 to 10 cm H_2O) presented a decrease in pH (from 7.36 to 7.33) and at the same time a decrease in $FECO_2$ (from 4.8 to 4.2) at a constant $\dot{V}CO_2$. As decreasing $FECO_2$, implies reduction of $PaCO_2$ and hence increase in pHa, the model did not describe this behavior.

The appendix B, includes plots of measured and simulated fR, pHa and $FECO_2$, for each of the twelve patients, similar to those presented in chapter 5 describing patients in ACV.

Table 6-2. Values of WRSS between measured data and model simulations for the different levels of PS.

Patient	1	2	3	4	5	6
High PS	*	0.02†	*	0.45	0.01†	11.05
	0.76	0.03†	*	0.65	0.03†	0.11
	0.10	0.01†	6.81	0.00†	0.02†	1.11
	0.43	0.00†	1.53	0.00†	0.74	0.71
Low PS	0.01	0.00†	2.73	0.01†	0.14	8.85
∑(WRSS) χ^2	1.30	0.06	11.07	1.12	0.95	21.82
test p	0.99	0.99	0.27	0.99	0.99	0.11

* Missing VT step changes due to patient outside protocol defined ranges.
† WRSS value calculated including estimation of fM.

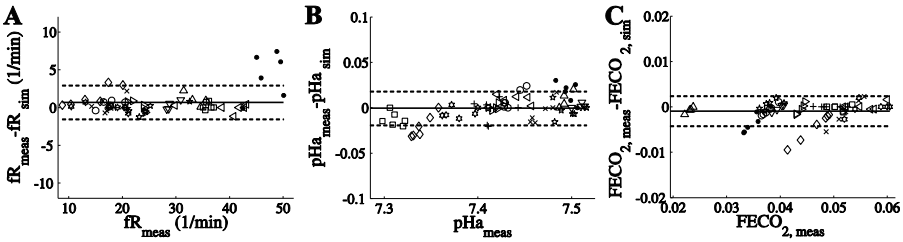

Figure 6-4. Bland-Altman plots of difference between measured and simulated patient response to changes in PS. Each symbol illustrates a single patient i.e. right-pointing triangle (patient 1), vertical cross (patient 2), upwards triangle (patient 3), hexagram (patient 4), square (patient 5), diamond (patient 6), circle (patient 7), downwards triangle (patient 8), diagonal cross (patient 9), left-pointing triangle (patient 10), dot (patient 11) and pentagram (patient 12). The solid lines illustrate the bias between measured and simulated values, and the dashed lines illustrate the limits of agreement. Each plot illustrates differences between measured and simulated fR (A), pHa (B) and $FeCO_2$ (C).

6.4. CONCLUSION

This chapter presented the evaluation of the set of models describing respiratory drive performed with a clinical protocol in which patients were ventilated in PSV. The set of models describing the respiratory drive adequately described patients' response in terms of blood acid-base status (pHa) pulmonary gas-exchange ($FECO_2$), and respiratory control (fR) to changes in PS. This being despite patients presented a range of different

Table 6-2. Values of WRSS between measured data and model simulations for the different levels of PS (continuation).

Patient	**7**	**8**	**9**	**10**	**11**	**12**
High PS	0.56	*	0.04	0.00†	43.96	0.20
	0.89	*	4.64	0.08	55.05	0.36
	0.48	0.05	0.16	0.01†	36.57	1.56
	0.07	0.97	0.21	0.01†	2.61	0.21†
Low PS	0.02	0.03	0.53	0.18	15.27	0.62
$\sum$(WRSS) χ^2	2.02	1.05	5.58	0.28	153.5	2.96
test p	0.99	0.99	0.99	0.99	0	0.99

* Missing VT step changes due to patient outside protocol defined ranges.
† WRSS value calculated including estimation of fM.

physiological and clinical conditions, including BE, RASS score, and days on mechanical ventilation.

The set of models was shown to be consistent with the results from the previous study performed in ACV. This may illustrate that the set of models are appropriate to describe patients' response in both ventilation modes. The major difference between the two studies was the addition of a model describing changes in Ceff. Ceff should be interpreted as the relationship between the level of PS and the VT generated by the sum of the two driving pressures i.e. the negative pressure generated by patient effort (Pmus) and the positive pressure delivered by the ventilator (PS).

The development of a set of physiological models that can be tuned with clinically available data to describe patients' response to changes in the level of ventilator support, has been presented. This set of models is limited and includes several assumptions that have to be considered. Nevertheless, the set of models adequately described the effects of changing the level of ventilator support in patients' fR, pHa and $FECO_2$, in two ventilation modes ACV and PSV. The next chapter, presents a critique of the set of models, additional findings and future work.

CHAPTER 7. DISCUSSION

Chapters 5 and 6 presented the results of two clinical protocols that were performed to evaluate the set of models ability to describe patients' response to changes in VT and PS respectively. The set of models were used to simulate patients' response in terms of fR, pHa, and $FECO_2$, and then compared against measured data. In both protocols, the set of models adequately described patients' response, with similar bias and limits of agreement. This chapter presents a discussion of the set of physiological models developed in this PhD thesis and their evaluation. Section 7.1 presents a summary of the problem addressed and the major findings of this thesis. The secondary findings of this thesis are presented in section 7.2. Models' assumptions and limitations of the evaluations are presented in section 7.3. The future work using the models integrated in this thesis is addressed in section 7.4. The final conclusions are presented in section 7.5.

7.1. MAJOR FINDINGS

Selecting adequate ventilator settings to manage patients on assisted ventilation modes is difficult. Patients may respond in different ways to changes in settings of mechanical ventilation, depending upon their underlying physiological state. Understanding patients' physiology is therefore necessary to adequately select ventilation settings. Providing adequate ventilation may reduce the deleterious effects of mechanical ventilation, reduce mortality, increase patient safety, promote patients synchrony with the ventilator, and perhaps reduce the length of stay on mechanical ventilation. For these reasons, clinical and technological solutions have been developed to assist physicians to set adequately ventilation settings. The clinical solutions include general guidelines like the ARDSNetwork guidelines for mechanical ventilation. The use of these guidelines has shown to reduce the risk of mortality and development VILIs (32,53), but do not provide further description about patients' physiology. Nevertheless, these guidelines are a first attempt to individualize ventilator settings.

Technological solutions can either automatize reduction in ventilator support and even select levels of FIO_2 and PEEP according to established clinical guidelines (44,46,51,52) or describe specific patients' response through model simulations and provide advice upon setting mechanical ventilation considering the detrimental effects of mechanical ventilation. The latter type

of technological solution includes systems like SOPA (80,97), NPS (36,92), "beat to beat" (35,88), CP (84,85), and INVENT (1,6), systems which are under development, and aim to describe individual patients' physiology, enabling simulation of individual patients' response to changes in mechanical ventilation settings.

The approach of these model-based systems is to integrate models describing different physiological processes involved in ventilation i.e. pulmonary gas-exchange, blood acid-base status, circulation, body buffering, respiratory control, and lung mechanics. In this way, the effects of each of these processes can be combined to describe and simulate patients' response to changes in ventilator settings. In chapter 2 it was shown that, the set of physiological models included in INVENT, meets 7 requirements that allow description and simulation of patients' pulmonary gas-exchange, ventilation and blood acid-base status at the bedside (section 2.1.3). Despite the variety of models similar to the set of models included in INVENT, there appear to be no technological solution which have both increased model complexity and where the more compex models can be tuned to the individual patient at the bedside.

Prior to this thesis, INVENT was limited to describing patients in controlled ventilation modes. This represented a major limitation since the majority of patients receiving mechanical ventilation are ventilated in assisted ventilation modes (7,8). As integrating a model of respiratory control into INVENT was thought to enable the description of spontaneously breathing patients, the aim of this PhD thesis was therefore to integrate a model of respiratory control into INVENT's set of physiological modes, and evaluate the integrated model capability to describe patients' response to changes in the level of ventilator support i.e. VT or PS.

For this reason, a review of models of respiratory control was performed to identify a suitable model of respiratory control. The model of chemoreflex breathing control of Duffin, which includes a detailed model of the CSF acid-base status (103) that could be used to modulate patients' respiratory response was selected. This model of respiratory control required two adaptations before being integrated into INVENT, including a condition allowing down-regulation of the two chemoreflex drives (Dp and Dc) (131-133), and calibration of the CSF acid-base status in relation to mixed venous blood (136). These adaptations were necessary to enable description of patients on mechanical ventilation, which may present abnormal blood-acid base conditions.

The set of models describing respiratory drive, required two additional models to describe and quantify: the situation where patients cannot satisfy $\dot{V}Aexp$

due to respiratory muscles failure; and the increase in patient effort on reduction of PS to compensate the lack of support. The set of models were evaluated with two clinical protocols, performed in ACV or PSV, respectively. These ventilation modes provide either VT or PS to the patient, and as such the patients' response to changes is support is different. When VT is fixed, patients are able to modulate only fR as response to changes in VT (10). Conversely, when PS is fixed, patients are able to modify both VT and fR. Patients ability to modify VT when ventilated in PSV is due to patient effort (19,20).

The major finding of this PhD thesis was that when integrating physiological models of pulmonary gas-exchange, blood acid-base, body buffering, respiratory control, CSF acid-base, muscle function and effective compliance, it is possible to adequately describe and simulate patients' response to changes in VT and PS. Model simulated and measured values of fR, pHa, and $FECO_2$, showed little bias, and limits of agreement were within that which one might consider clinically relevant. These results were similar for both of the two protocols.

Integrating models to describe the relationship between ventilation, pulmonary gas-exchange, blood acid-base status, body buffering, and respiratory control, and simulate patients' response to changes in levels of ventilator support has not been done before. However, different models have been developed to: a) describe the effects of changing FIO_2 or/and $FICO_2$ in healthy subjects (102,103); b) understand a specific physiological process in relation to changes in ventilation, such as cerebral blood flow (102,134), functional residual capacity (18), periodic breathing (118,120,122), respiratory control during exercise (104,121), or the effects of acclimation to altitude on respiratory control (123,146); c) describe only pulmonary gas-exchange or/and lung mechanics during mechanical ventilation (34,147); or d) describe and simulate patients on mechanical ventilation with a combination of physiological model components (including pulmonary gas-exchange, blood acid-base status, and lung mechanics) and either black-box control system models, fuzzy logic algoritms or optimization algorithms (36,77,80,84,85,88,92,97). Describing patients' response to changes in mechanical ventilation is a complex process because depends upon the combined effects of several physiological processes, in particular during assisted ventilation where patients are spontaneously breathing. The results from the studies conducted for evaluating the set of models described here, have shown that by integrating physiological models it is possible to describe patients' response to changes in the level of ventilator support in terms of pulmonary gas-exchange, blood acid-base status, and respiratory control. The importance of adequately describing patient's response, may enable

simulation and prediction of patients' response to changes in VT or PS, required for providing advice on mechanical ventilaton settings.

Describing and quantifying the way patients respond to changes in the level of ventilator support (VT or PS) with physiological models of this complexity is novel. There are, however, descriptive studies where patients have been ventilated at different PS levels. These studies have reported the effects of changing PS among patients with several pathologies (18,21,30,42,138,148), and have compared PS with other ventilation modes, e.g. intermittent mandatory ventilation (IMV) (149), synchronized intermittent mandatory ventilation (SIMV) (144), proportional assist ventilation (PAV) (145), and neurally adjusted ventilatory assist (NAVA) (56). The reported patient response among these studies, shows similar responses in fR and VT as shown in the studies of this thesis (figure 6-1 A-B). However, these previous studies did not evaluate the acid-base response to changes in ventilation, neither in terms of $FECO_2$ or arterial blood, neither have they described patient response using a set of models including relevant physiological systems. In addition, the clinical studies conducted for presenting this work, have shown that patients respond to changes in VT and PS even when they are relatively small (i.e. 50 ml or 2 cm H_2O), and patients' responses to these changes are measurable in terms of fR, pHa and $FECO_2$. Interestingly, a significant shift in blood acid-base status due to either decrease or increase of $\dot{V}Apat$ can be suspected only by noting an increase or decrease in $FECO_2$ higher than 0.25%. Other studies have described patients' response to increased $FICO_2$ (i.e. a hypercapnic challenge). The purpose of such studies was to identify difficult to wean patients by measuring the increase in airway occlusion pressure ($P_{0.1}$) during the hypercapnic challenge (150,151). These studies did not describe the relationship between ventilation, pulmonary gas-exchange and blood acid-base status. The clinical studies and data have shown that instead of hypercapnic challenges, relatively small reductions in the level of ventilator support are enough to increase the respiratory response. The results from the work presented here can therefore be seen as novel when compared to previously performed studies.

7.2. SECONDARY FINDINGS

In addition to adequately describing patients' response to changes in the level of ventilator support, there were several interesting additional findings, these being presented in the following sub-sections. Sub-section 7.2.1 presents the two patient-specific respiratory control model parameters. Subsection 7.2.2 presents the level of model-input complexity required to describe patient response. Section 7.2.3 presents different $\dot{V}O_2$, and $\dot{V}CO_2$ responses on reducing VT and PS. Finally, in subsection 7.2.4, Vds calculated with the

method presented in section 3.3 is shown to correlate with an alternative method tp estimation of serial dead space considering re-breathed CO_2.

7.2.1. PATIENT-SPECIFIC RESPIRATORY CONTROL MODEL PARAMETERS

In order to describe and simulate patients' response to changes in ventilator support, all model parameters must be tuned to individual patients' conditions. For the set of models previously included in INVENT, all patient-specific model parameters (fs, fA2, f2, BE, DPG) have been characterized, estimated and shown to describe patients' response. However, patient-specific parameters of the respiratory control model (SIDcsf and TC) were estimated, characterized, and proven to describe patients' respiratory response with the two studies conducted for this work.

The respiratory control model has two components, CSF acid-base model (figure 3-4 D) and chemoreflex respiratory control equations (figure 3-4 E). These components can be described with parameters SIDcsf and TC, respectively. According to the results of the two conducted studies, it has been shown that both parameters can be tuned and are uniquely identified for individual patients. Tuning parameter SIDcsf was possible with the addition of equation 11 to the CSF acid-base model, assuming that CSF bicarbonate can be determined from mixed venous blood bicarbonate. Tuning parameter TC was possible with equation 21, assuming adequate muscle function (fM=1), and determining $\dot{V}$Apat from clinical data, as described in section 4.3. Both parameters have an effect on respiratory control, SIDcsf modulates [H^+csf] and Dc (108,109), while TC is determined by the current pHa.

7.2.2. MODEL-INPUT COMPLEXITY REQUIRED TO DESCRIBE PATIENT RESPONSE

In addition to identifying patient-specific parameters, the set of models requires inputs to describe and simulate patients' response. Identifying the minimum number of model-inputs to adequately describe patients's response is required as part of the characterization and evaluation of the set of models. For that purpose, the set of models was firstly evaluated in a study conducted with patients ventilated in ACV (fixed levels of VT) in order to isolate patients' response to changes in fR as VT was modified (20). In this way, the model-input complexity necessary to evaluate patients' response was determined without influence of patient effort. Figures 5-1 and 5-2, illustrate that the model-input complexity for adequately describe and simulate fR, pHa and $FECO_2$, includes changes in Vds, $\dot{V}CO_2$, and fM, as shown in table 5-2. The

same model-input complexity was also required to describe patients at ventilated at different levels of PS, with the addition of Ceff.

7.2.3. DIFFERENT $\dot{V}O_2$ AND $\dot{V}CO_2$ RESPONSES ON REDUCING VT AND PS

The studies conducted gave interesting results in relation to patients' metabolic response on changing ventilator support. Patients' response in terms of $\dot{V}O_2$ and $\dot{V}CO_2$ was different in modification of VT or PS. 50% of the patients ventilated in ACV (patients 1, 5, 6, 8, 9, 10) presented a systematic increase in $\dot{V}O_2$ and $\dot{V}CO_2$ as VT changed, in contrast patients ventilated in PSV did not present changes in $\dot{V}O_2$ and $\dot{V}CO_2$ as PS changed. The lack of a systematic change in $\dot{V}O_2$ or $\dot{V}CO_2$ in PSV contrasts with a previous study performed in PSV where systematic increases in $\dot{V}O_2$ were observed on decreasing PS (21). This difference in $\dot{V}O_2$ response between the studies may be due to the smaller PS step-changes and range of PS modification used in the PSV study, which were about the half of those used by (21). The larger increases in $\dot{V}O_2$, and $\dot{V}CO_2$ on VT reduction may be consistent with the increased work of breathing and reduced synchrony during ACV in comparison to PS (20,41,144).

7.2.4. CORRELATION BETWEEN TWO SERIAL DEAD SPACE CALCULATIONS

The values of serial dead-space estimated in the studies were particularly interesting in the PSV study. Here patients occasionally presented with high values of Vds (figure 6.3). To confirm whether these estimates were correct these values were compared to calculations performed using Fowler's method (Vdf) (152), and taking re-inspired CO_2 into account as described previously (153,154). Figure 7-1 A illustrates the relationship between VT and Vds. The grey symbols in figure 7-1 A represent values of Vds calculated using the method presented in this thesis. The black symbols in figure 7-1 A represent Vdf. Both, Vds and Vdf increase linearly as VT increases. The r-values for the correlation between VT and serial dead space calculations were r-value=0.79 ($p<0.001$) for Vds, and r-value=0.87 ($p<0.001$) for Vdf. Figure 7-1 B illustrates Bland-Altman analysis for both calculations of serial dead space showing bias of -17 ml and limits of agreement of ±70 ml.

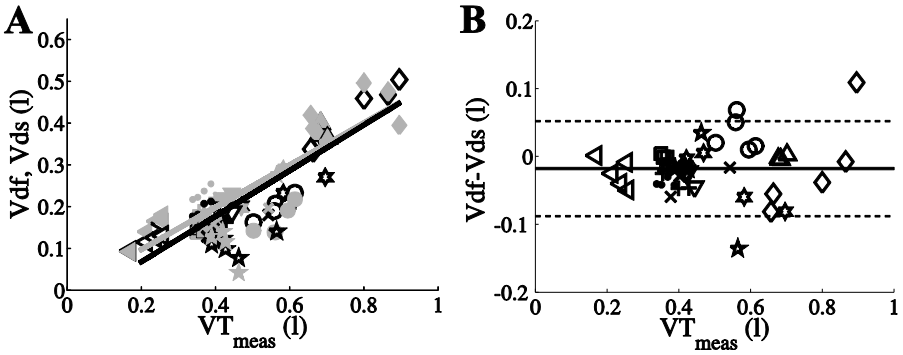

*Figure 7-1. Serial dead space estimated at each PS level. A) Serial dead space is plotted against VT for each patient at each PS level. Grey symbols illustrate serial dead space calculated with equation 15 (Vds) and black symbols illustrate serial dead space calculated with Fowler's method corrected to rebreathed CO_2 (Vdf). The grey and black lines illustrate the correlation between each serial dead space calculation and VT. Vds=0.48*VT-0.01 l, r-value=0.79 (p<0.001) and Vdf=0.53*VT-0.04 l, r-value=0.87 (p<0.001). B) The agreement between Vds and Vdf is shown with a Bland-Altman plot. The solid line illustrates the bias between Vds and corrected Fowler's dead space, the dashed lines illustrate the limits of agreement. Each symbol illustrates a single patient i.e. right-pointing triangle (patient 1), vertical cross (patient 2), upwards triangle (patient 3), hexagram (patient 4), square (patient 5), diamond (patient 6), circle (patient 7), downwards triangle (patient 8), diagonal cross (patient 9), left-pointing triangle (patient 10), dot (patient 11) and pentagram (patient 12).*

7.3. LIMITATIONS OF THE SET OF MODELS DESCRIBING RESPIRATORY CONTROL

The set of models describing the respiratory drive developed and evaluated in this thesis was designed to be tuned with clinically available data, thus several assumptions were necessary to simplify the models such that parameter values could be estimated uniquely. In addition, to the model assumptions, the clinical studies for evaluating of the set of models were limited due to practical problems when perfoming the clinical studies. Sub-section 7.3.1 presents model assumptions and sub-section 7.3.2 presents limitations of the evaluations.

7.3.1. RESPIRATORY CONTROL MODEL ASSUMPTIONS

The advantage of using simple models for describing physiological processes is that they can be tuned with clinically available data. The purpose of doing so is to allow these models to be used at the bedside without the need for complex measurement technology, to describe and simulate patients' response. However, using simple models requires uniquely identifiable model parameters. The respiratory control model requires arterial and CSF [H^+], $PaCO_2$, and PaO_2 to simulate ventilation (103). However, factors like cerebral blood flow (CBF), afferent neural inputs and sedation or/and state of consciousness may influence the respiratory control model. Thus, the set of models was used to perform simulations of patient response under the following assumptions: steady state ventilation; constant cerebral blood flow; no influence from afferent neural inputs; constant state of consciousness; and ventilation at baseline conditions is adequate.

- **Steady state ventilation**. The set of models was used to perform steady state simulations describing fR, pHa and $FeCO_2$ on changing VT or PS, and assuming steady state conditions of Vds, $\dot{V}CO_2$, and fM. The differences between patients' response simulations for each level of ventilator support are due to changes between steady state conditions upon the corresponding level of ventilator support, as illustrated in figures 5-1, 5-2, and in appendices A and B. Substantial information representing dynamic state is present in data measured following changes in VT or PS, however, this has not been exploited.

- **Constant cerebral blood flow (CBF).** Fluctuations in CBF are induced by changes in $PaCO_2$ or [HCO_{3a}^-] (11,134). For instance, increased CBF generates a sudden reduction of $PcsfCO_2$, which may reduce [H^+csf] and Dc. Reduced Dc may down-regulate Dp producing central apnea during unconscious breathing (i.e. Dw=0 l/min). Thus, fluctuations in CBF may generate an intermittent mismatch between Dc and Dp, triggering the Cheyne-Stokes breathing pattern i.e. alternating periods of apnea followed by periods of high fR (110,118,120,122). The effects of changes in CBF were not considered, assuming CBF as a constant (table 3-1). Consideration of changes in CBF may result in conditions that perhaps do not reach steady state ventilation.

- **Afferent neural inputs.** The effect of afferent neural inputs from pulmonary stretch receptors on ventilation is an increase of the neural expiratory time in conditions of high inspiratory flow, so that, fR is reduced. This effect is also known as the Hering-Breuer reflex (155). The effect of afferent neural inputs were not considered in the

models, however, this effect might be identified as a reduction of fR on increasing the level of ventilator support.

- **Constant state of consciousness.** Steady state ventilation is affected by the state of consciousness and administration of sedatives. For example, administration of opioids can shift the respiratory response to CO_2 by increasing TC, and consequently reducing the central chemoreflex respiratory drive (Dc) (135,156). In this way, TC may include the effects of sedation. Changes in patients' state of consciousness over a longer time period, e.g. following modification of opioid therapy, would require re-estimation of TC.

- **Ventilation at baseline conditions is adequate.** The parameter describing patient's muscle function (fM), indicates whether patients respond inadequately to changes VT or PS. However, to calculate this parameter, baseline ventilation was considered as adequate. Inadequate response to changes the level of ventilator support was assumed as the mismatch between calculated $\dot{V}$Apat and model simulated $\dot{V}$Aexp. Accordingly, fM=1 describes patients' ability to generate $\dot{V}$Aexp on modification of ventilator support. fM is only estimated as different from 1 when the absolute difference between model simulated and measured values of $FECO_2$ is greater than 0.25%, i.e. the standard deviation of $FECO_2$ in healthy subjects (141). The causes of inadequate patient response or respiratory muscles failure cannot be determined with the set of models, so it is unknown whether fM<1 represents fatigue, reduced strength or endurance, or poor muscle firing (17,21,31). On the contrary, fM>1 may indicate an improvement in ventilation, as $\dot{V}$Apat is higher than $\dot{V}$Aexp. In case of fM>1 on increasing PS, increased $\dot{V}$Apat may be related to respiratory alkalosis due to over-support (42), thus the interpretation of fM>1 should be complemented among Ceff and changes in fR.

7.3.2. LIMITATIONS OF CLINICAL STUDIES

Evaluating the set of models in the clinical practice requires taking into account several limitations due to practical problems when performing the protocols. These limitations are in relation to: time; type and number of enrolled patients; and availability of measurements.

- **Time-related limitations.** The clinical studies were performed in patients in assisted ventilation. The protocols were designed to evaluate patients' response to changes in ventilator support, thus, only 15 minutes per level of support were considered, in order to

allow the patient to reach steady state ventilation. The evaluation time was therefore limited to 60 to 75 minutes. During this period of time the set of models described adequately patients' response. However, this time is less than typical ICU stay. The model evaluation was limited to a short period of time, so that, the time required for re-estimating the set of models parameters has not been determined.

- **Patient-related limitations.** The number of patients enrolled into the two clinical studies was limited to 15 patients per study. In addition, the enrolled patients presented different diagnoses and physiological conditions. The evaluation of the set of models was therefore limited to a relatively small sample size, and heterogeneous patient group. Nevertheless, the models provided adequate description of patients' response, and hence showed the capability of describing general ICU patients in assisted ventilation modes.

- **Measurement-availability limitations related to tuning model parameters.** In order to describe patients' response to changes in ventilator support, models parameters require to be tuned to individual patients' conditions. For that purpose, a number of measurements are required. These requirements are: determining cardiac output ($\dot{Q}$); measurements of $\dot{V}O_2$ and $\dot{V}CO_2$; performance of an experimental procedure involving 3-5 step changes in FIO_2; and a single measurement of arterial blood gases (ABG). $\dot{Q}$ is necessary to determine high and low $\dot{V}/\dot{Q}$ ratios describing the pulmonary gas-exchange (40). $\dot{Q}$ is seldom measured in ICU, thus it is estimated from the body surface area (BSA) and a fixed cardiac index (4). This calculation has been shown to be an adequate approximation for describing pulmonary gas-exchange (4). Measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ are also required to tune the pulmonary gas-exchange, blood acid-base and respiratory control models parameters. These measurements are performed with indirect calorimetry, which is not widely used in ICU. In addition, tuning the pulmonary gas-exchange model requires an experimental procedure in which the patient is subjected to 3-5 levels of FIO_2. Despite this process is semi-automatic requiring from the physician to perform changes in the level of FIO_2 in the ventilator, the experiment is performed in about 10-15 minutes (61,62). The model parameters of blood acid-base and respiratory control can be determined from a single ABG, which is measured at the beginning of the experimental procedure.

- **Measurement-availability limitations related to lung mechanics.** Measuring lung mechanics and work of breathing may provide a

complete description of patients' response. However, measuring work of breathing requires the use of an esophageal catheter to measure esophageal pressure (Peso). Peso is however seldom used in ICU. Accordingly, during the clinical studies performed to evaluate the set of models describing respiratory drive, Peso, was not performed. As such, measurements of airway pressure and flow were used to determine Ceff. The interpretation of Ceff was limited due to lack of measurements of Peso and work of breathing (57,58). Studies are required to evaluate whether the calculation of Ceff provides information compatable with that available from esophageal measurements.

7.4. FUTURE WORK

Through this thesis, the need of developing a set of models describing the respiratory drive that can be used at the bedside was explicit. The clinical application of the set of models is therefore a logical future development. There are however several interesting modelling issues that can be addressed in the future, these being: evaluation considering larger periods of time; evaluations considering specific patient groups; determining whether TC can quantify the degree of sedation; and determine whether Ceff can be used to quantify patients' effort on reduction of PS, and hence be used as a surrogate measurement of work of breathing.

So far, the set of models was evaluated over a relatively short time-period. It is not therefore known how often it is necessary to re-estimate model parameters, or how model parameters might change with time as the patient's condition varies. A long-period evaluation of the models may provide insight as to how often patients' conditions change, and what is a significant change necessary to re-tune the parameters.

Evaluating the set of models in patient specific group may provide insight into patients' progress during mechanical ventilation. In doing so, it might be possible to identify patterns of response and changes in model parameters within different patient groups e.g. ARDS, or postsurgical patients.

Long-period evaluations combined with different levels of sedation and analgesia may determine whether TC changes during sedation. If TC changes with sedation, it may be possible to use TC to determine the degree of respiratory drive depression due to e.g. opioid administration.

Determining whether Ceff can be used as a surrogate measurement of patient effort may require a study with simultaneous measurement of esophageal pressure to determine work of breathing and patient effort. In

doing so, the calculated portion of VT explained by patient effort can be calculated with both, esophageal pressure and Ceff. The comparison between both measurements will determine whether Ceff can be a surrogate measure of patient effort.

The set of models describing respiratory drive has been incorporated into the INVENT system, now commercialized as the Beacon Caresystem (Mermaid Care A/S, Nr. Sundby, Denmark). As such, the set of physiological models developed in this thesis is currently being used at the bedside, and several of the studies outlined above are now underway.

7.5. FINAL CONCLUSIONS

This PhD thesis has shown that the respiratory response of patients ventilated in ACV or PSV to changes in the level of ventilator support can be described with a set of physiological models including: pulmonary gas-exchange; blood acid-base status; body buffering; CSF acid-base status; chemoreflex respiratory control; and descriptions of muscle function and effective compliance. The model parameters required to describe respiratory control are SIDcsf and TC, at least for normal oxygenation. The set of models describing respiratory drive requires measurements of Vds, $\dot{V}CO_2$, fM and Ceff to adequately describe patients' response in terms of fR, pHa and $FECO_2$ on changing VT or PS. The set of models provided an adequate description of patients' response to changes in VT and PS, suggesting that the set of models may be appropriate for describing the effects of modifying ventilator support in ACV and PSV at the bedside.

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APPENDICES

Appendix A. Patients' measured and model simulated response to step changes in VT

Figures A-1 – A-6 illustrate patients' response to different levels of VT. Blank symbols and error bars represent measurements taken at different levels of VT. Grey symbols illustrate model simulated values considering changes in serial dead space (VD), CO_2 production ($\dot{V}CO_2$) and muscle function (fM). Each symbol represents a different VT level, i.e. baseline (upward triangles), first (circles), second (squares), third (diamonds), fourth (hexagrams) and fifth (downward triangles).

For each of the twelve patients included for data analysis (table 5-1), six plots are presented, arranged in two rows and three columns. The three plots of rows A in figures A-1 to A-6 illustrate the patients' measured and model simulated values of fR, pHa, and $FECO_2$ as VT was modified. The three plots of rows B illustrate the patients' measured changes in VD, $\dot{V}CO_2$ and muscle function (fM) as VT was modified.

For all patients, solid lines in row A, column 1 illustrate constant $\dot{V}A$, calculated assuming constant VD (dotted line in figures B1), constant $\dot{V}CO_2$ (dotted line in figures B2), and fM=1 (dotted line in figures B3). Values of fM lower than 1 indicate may inadequate patient response to reduction in ventilator support.

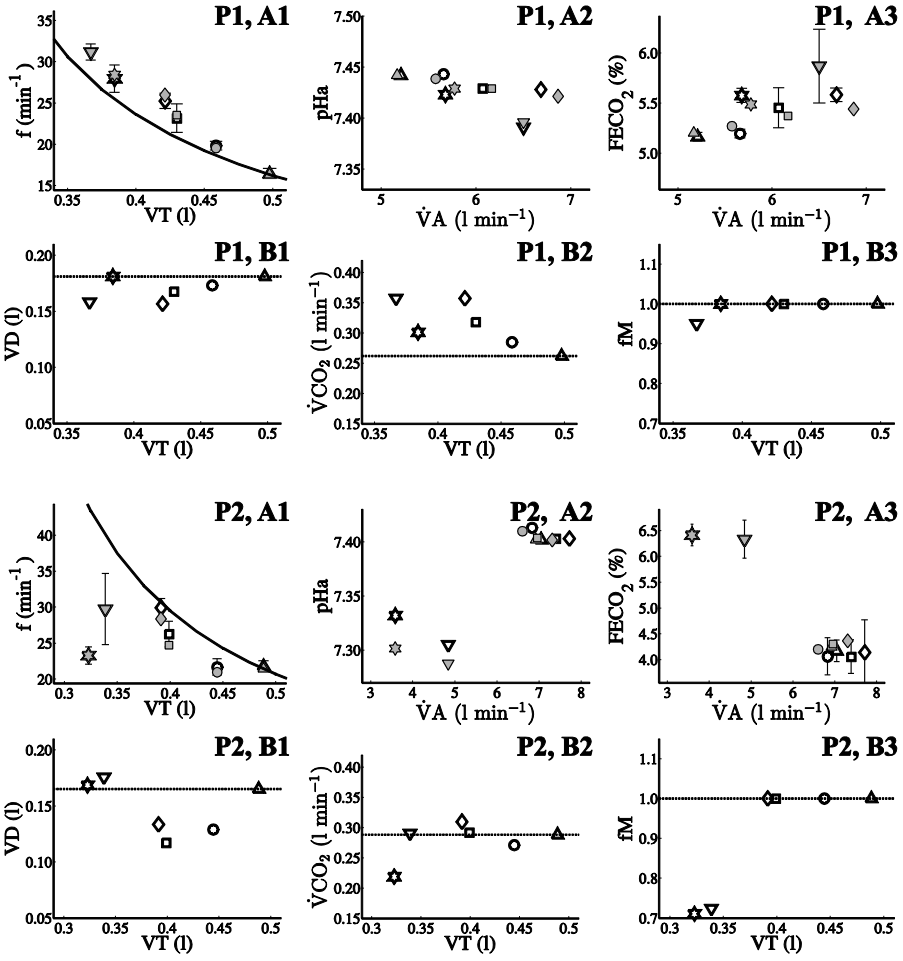

Figure A-1. Measured and model simulated patient response to changes in VT. Patients 1 and 2.

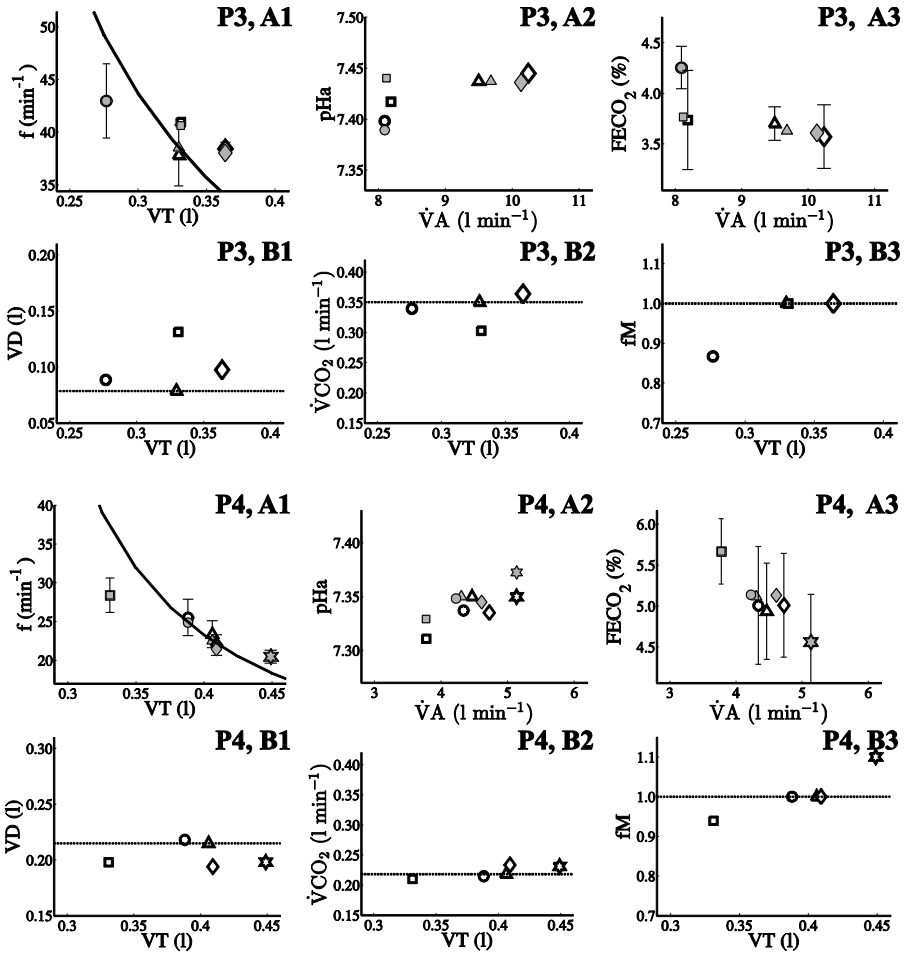

Figure A-2. Measured and model simulated patient response to changes in VT. Patients 3 and 4.

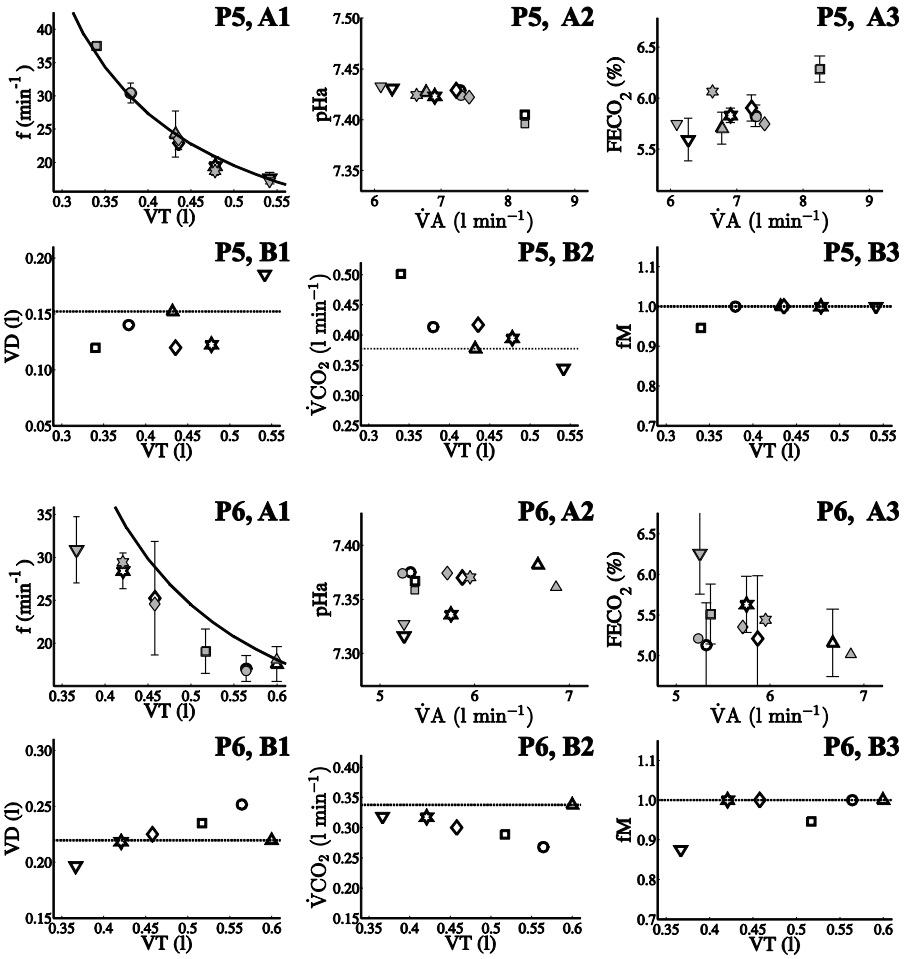

Figure A-3. Measured and model simulated patient response to changes in VT. Patients 5 and 6.

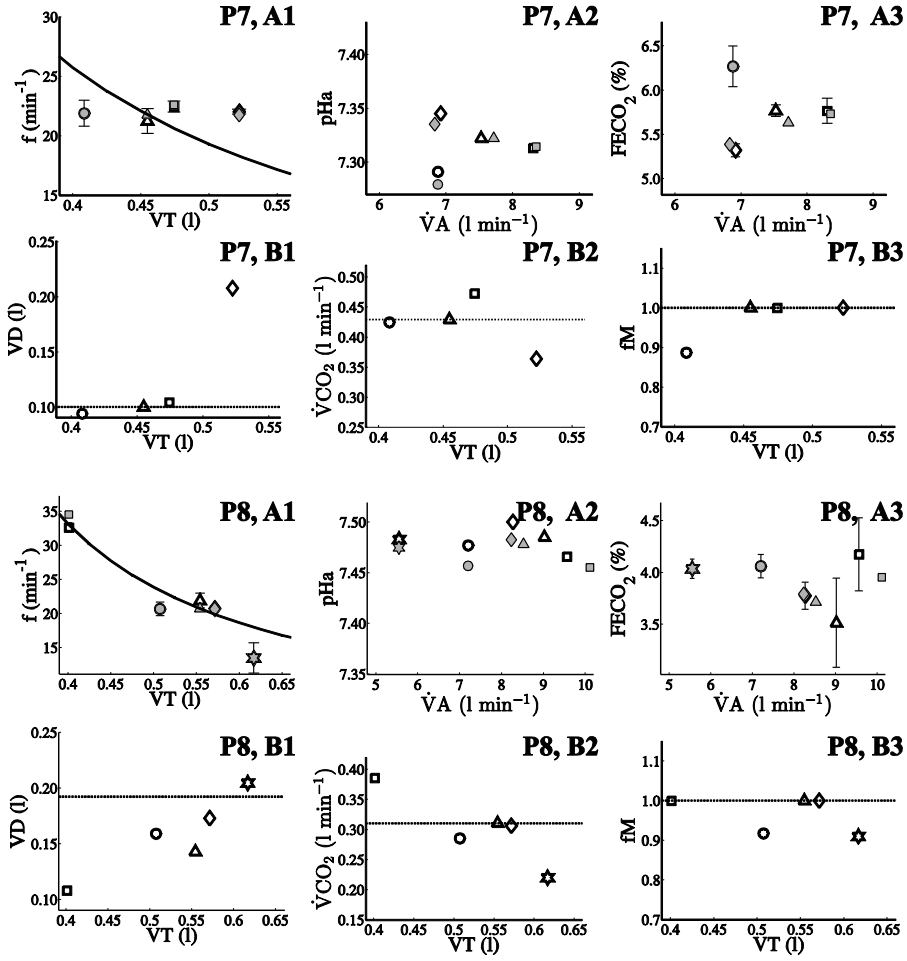

Figure A-4. Measured and model simulated patient response to changes in VT. Patients 7 and 8.

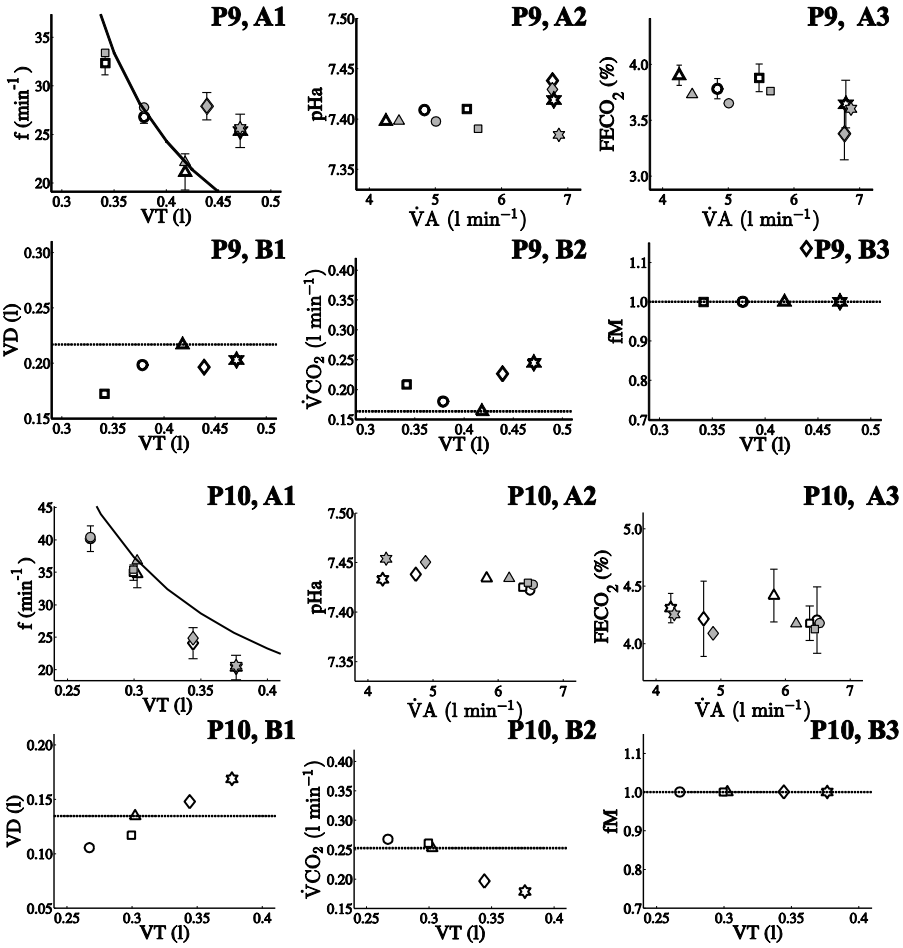

Figure A-5. Measured and model simulated patient response to changes in VT. Patients 9 and 10.

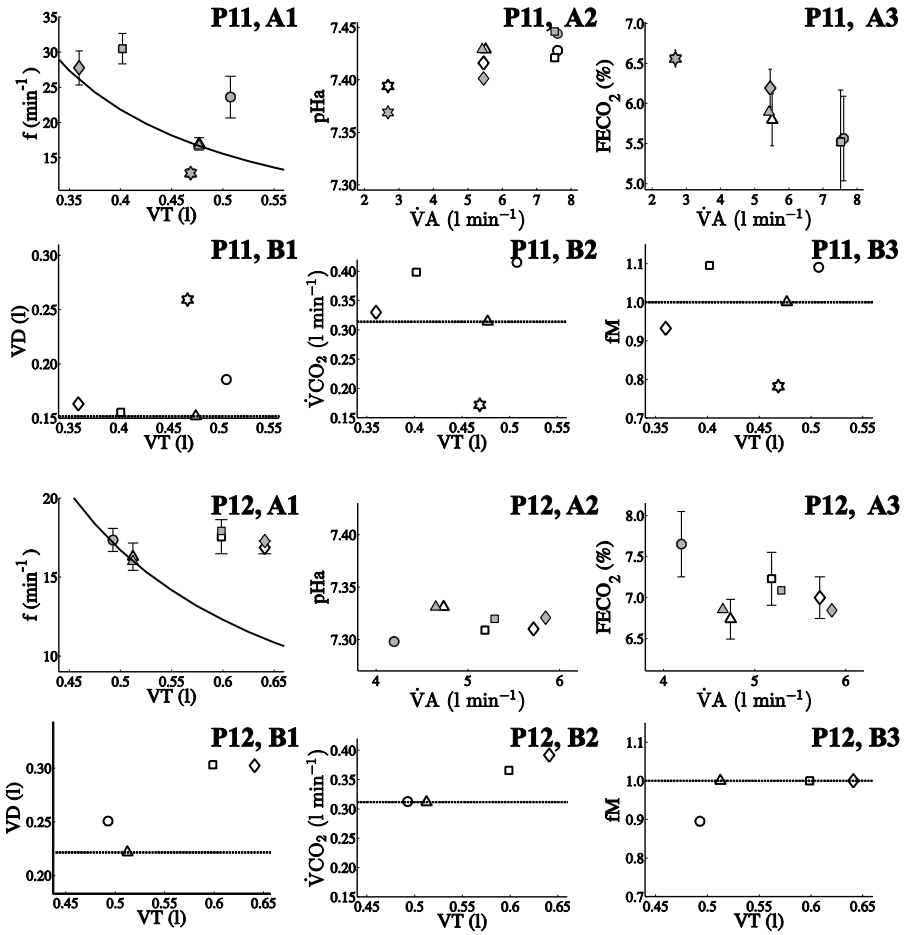

Figure A-6. Measured and model simulated patient response to changes in VT. Patients 11 and 12.

Appendix B. Patients' measured and model simulated response to step changes in PS

Figures B-1 – B-12 illustrate patients' response to different levels of PS. Blank symbols and error bars represent measurements taken at different levels of PS. Grey symbols illustrate model simulated values considering changes in serial dead space (VD), CO_2 production ($\dot{V}CO_2$) and muscle function (fM). Each symbol represents a different PS level i.e. baseline (upward triangles), first (circles), second (squares), third (diamonds), fourth (hexagrams) and fifth (downward triangles).

For each of the twelve patients included for data analysis (table 6-1), nine plots are presented, arranged in three rows and three columns. The three plots of rows A in figures B-1 to B-12 illustrate the patients' measured and model simulated values of fR, pHa, and $FECO_2$ as PS was modified. The three plots of rows B illustrate measured changes in VT, $\dot{V}A$ and Ceff at each PS level. Thre three plots of rows C illustrate the patients' measured changes in VD, $\dot{V}CO_2$ and muscle function (fM) as PS was modified.

For all patients, solid lines in row A, column 1 illustrate constant $\dot{V}A$ calculated assuming constant VD (dotted line in figures C1), constant $\dot{V}CO_2$ (dotted line in figures C2), and fM=1 (dotted line in figures C3). Values of fM lower than 1 may indicate inadequate patient response to reduction in ventilator support.

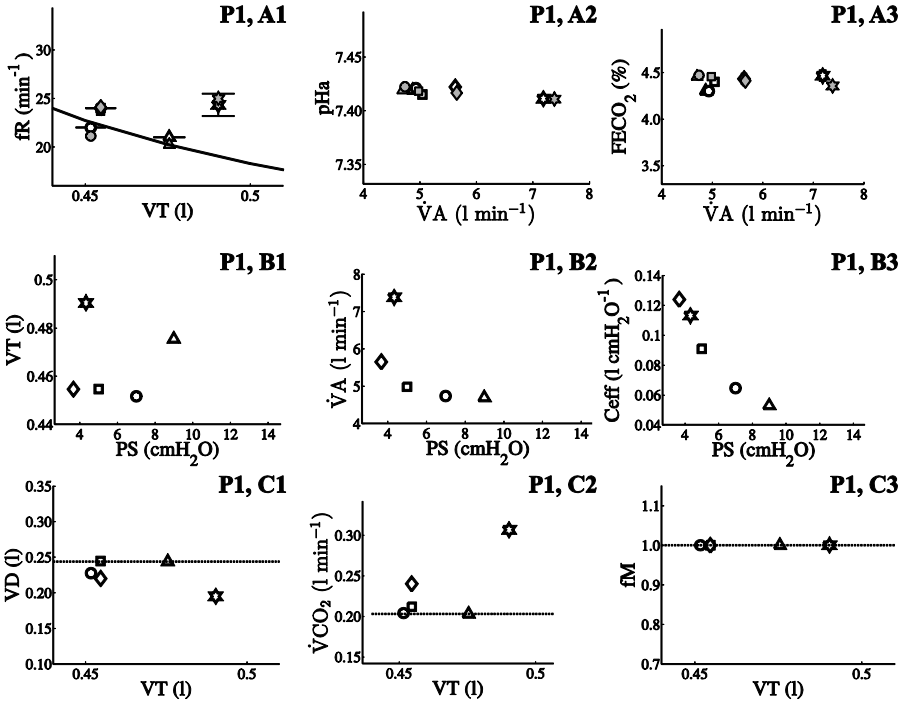

Figure B-1. Measured and model simulated patient response to changes in PS. Patient 1.

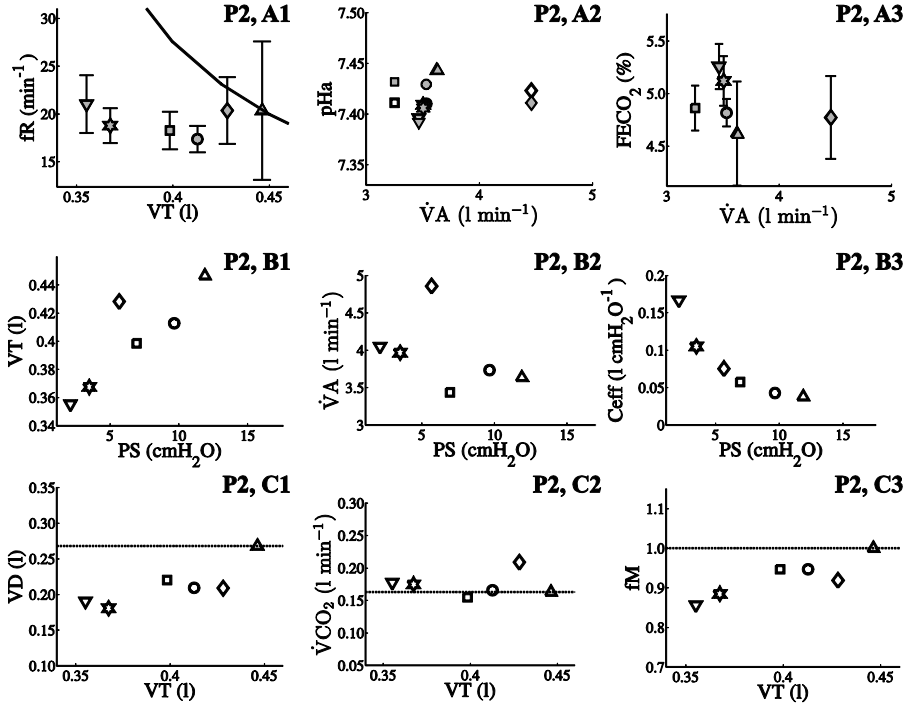

Figure B-2. Measured and model simulated patient response to changes in PS. Patient 2.

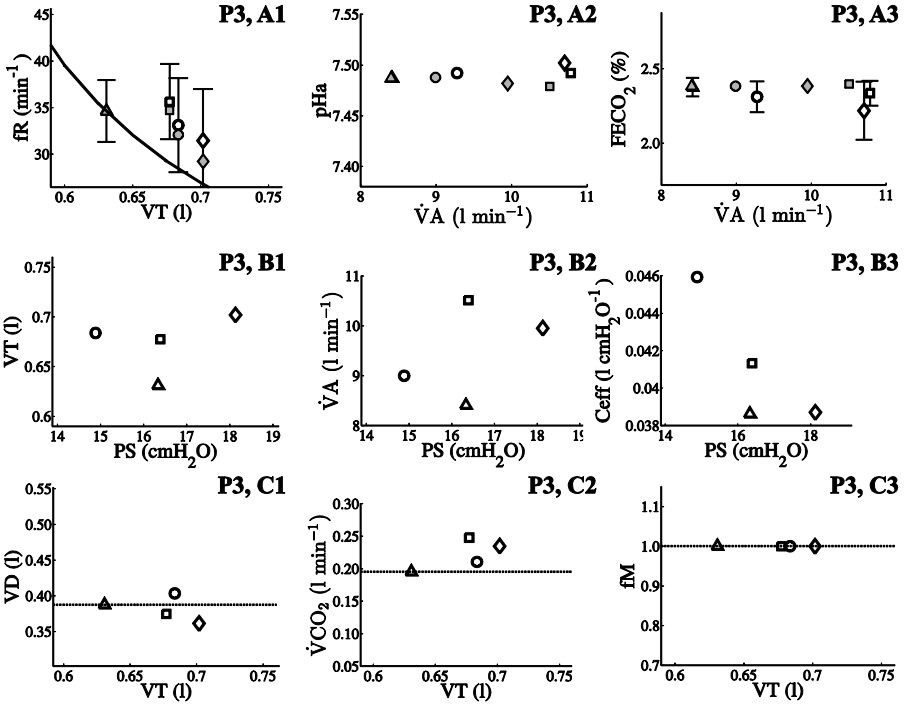

Figure B-3. Measured and model simulated patient response to changes in PS. Patient 3.

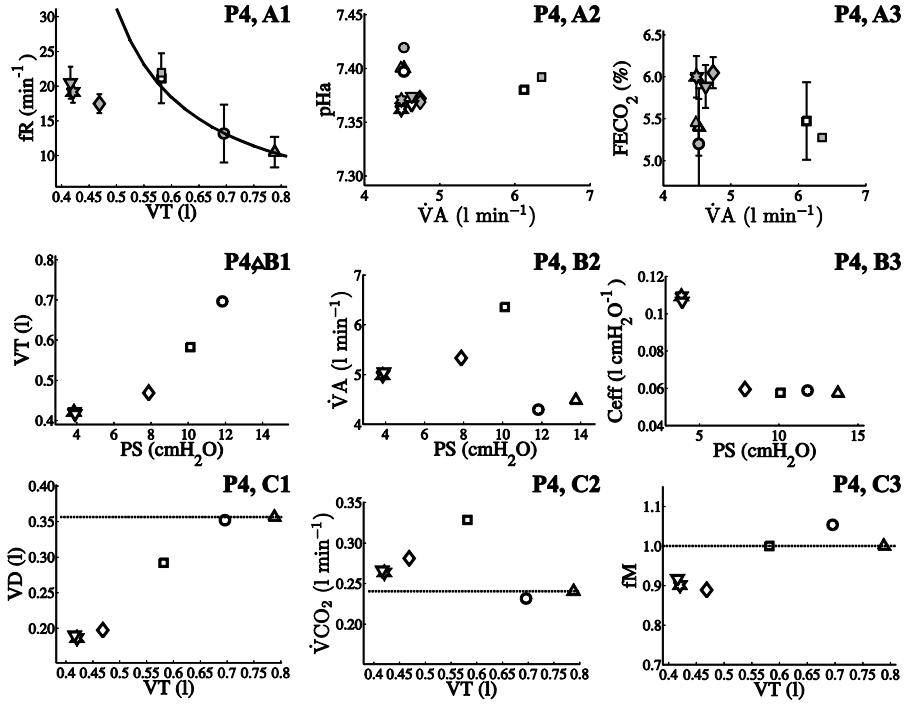

Figure B-4. Measured and model simulated patient response to changes in PS. Patient 4.

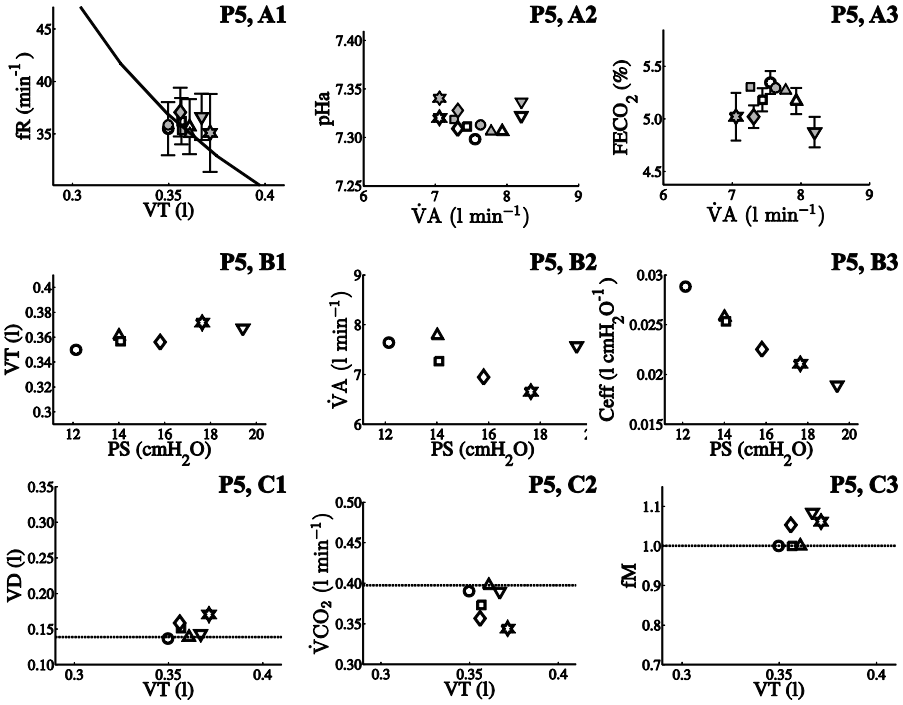

Figure B-5. Measured and model simulated patient response to changes in PS. Patient 5.

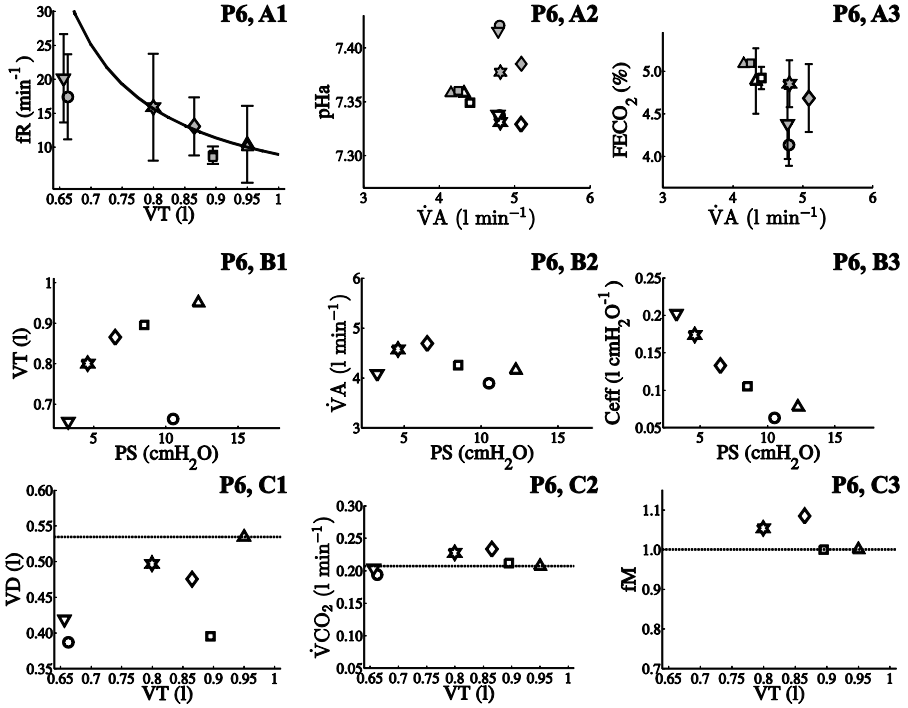

Figure B-6. Measured and model simulated patient response to changes in PS. Patient 6.

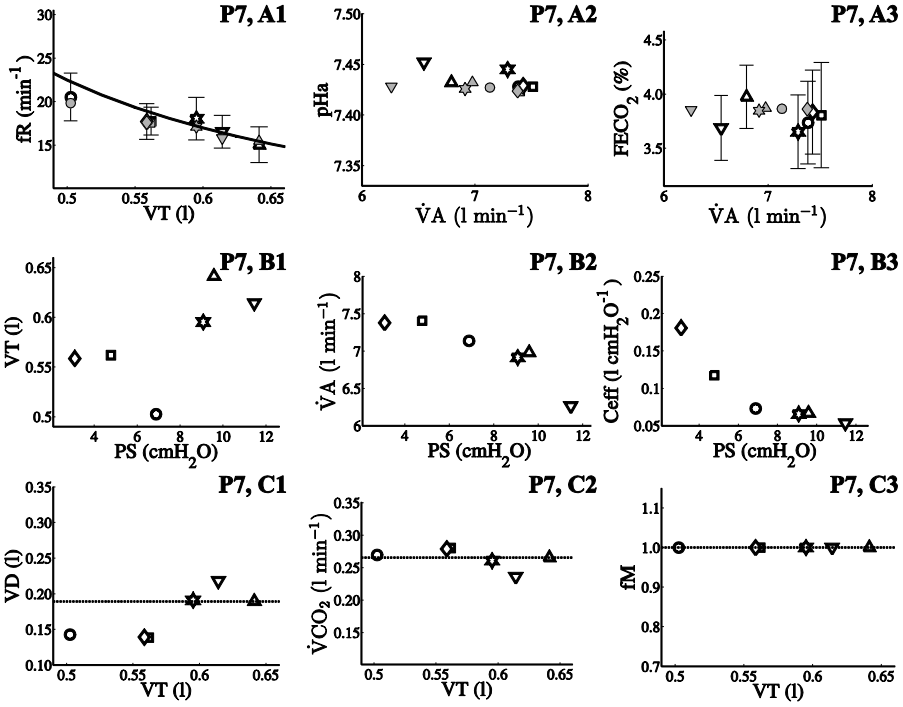

Figure B-7. Measured and model simulated patient response to changes in PS. Patient 7.

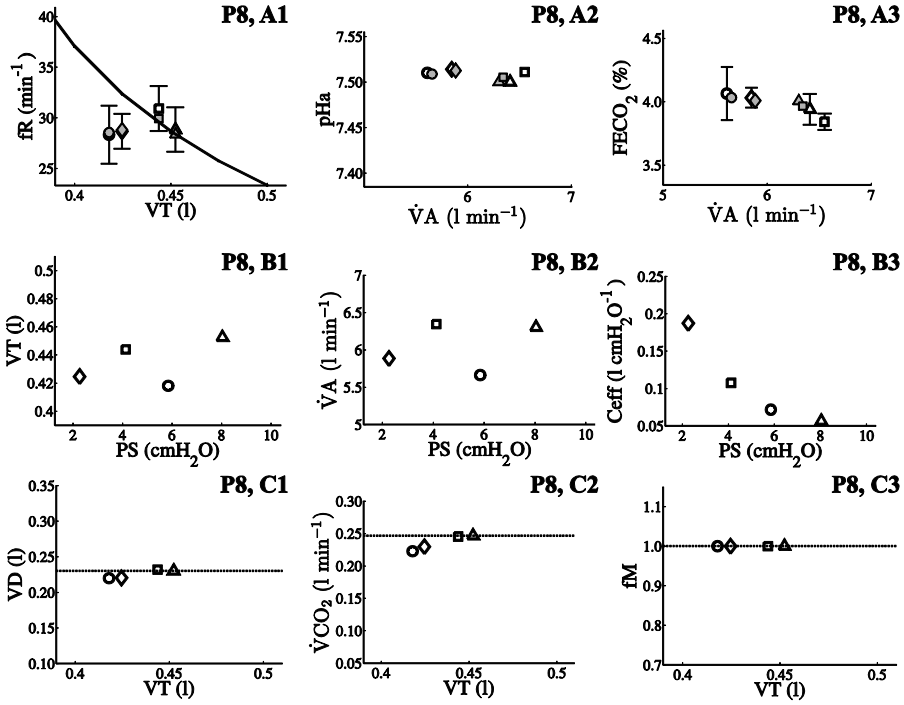

Figure B-8. Measured and model simulated patient response to changes in PS. Patient 8.

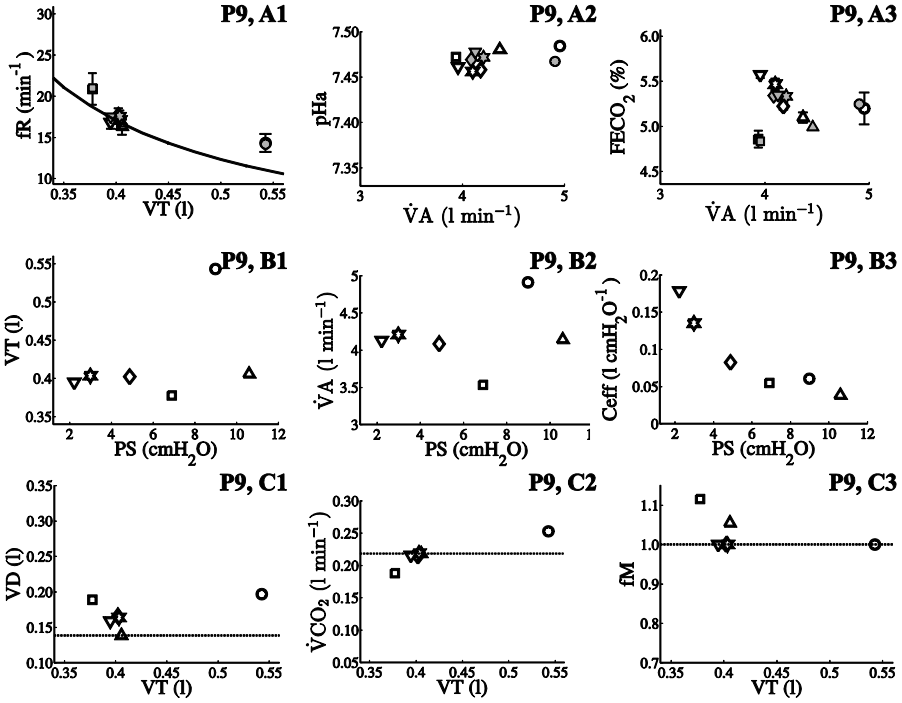

Figure B-9. Measured and model simulated patient response to changes in PS. Patient 9.

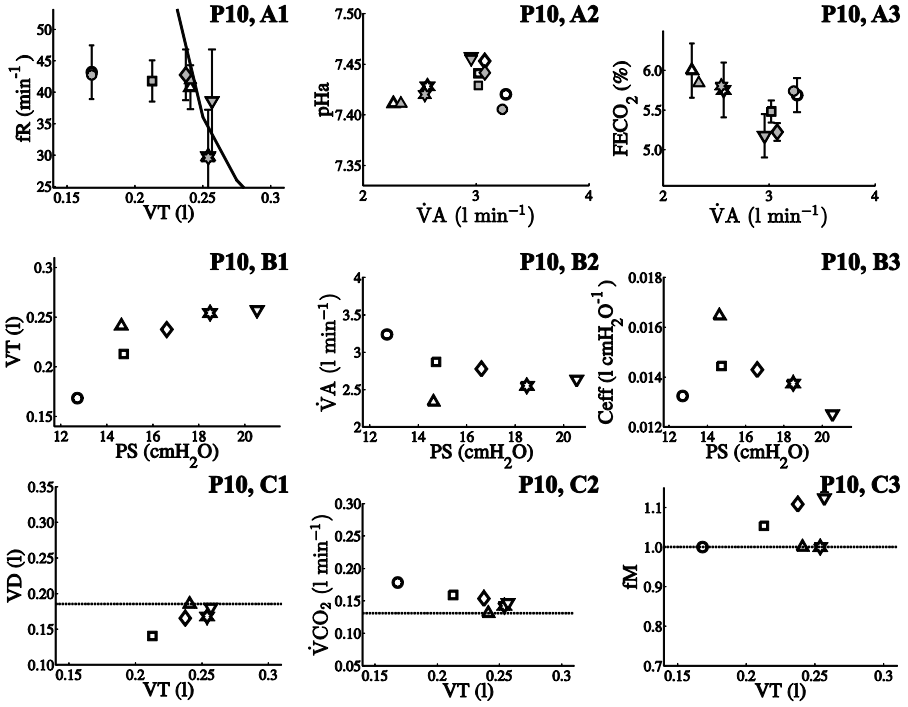

Figure B-10. Measured and model simulated patient response to changes in PS. Patient 10.

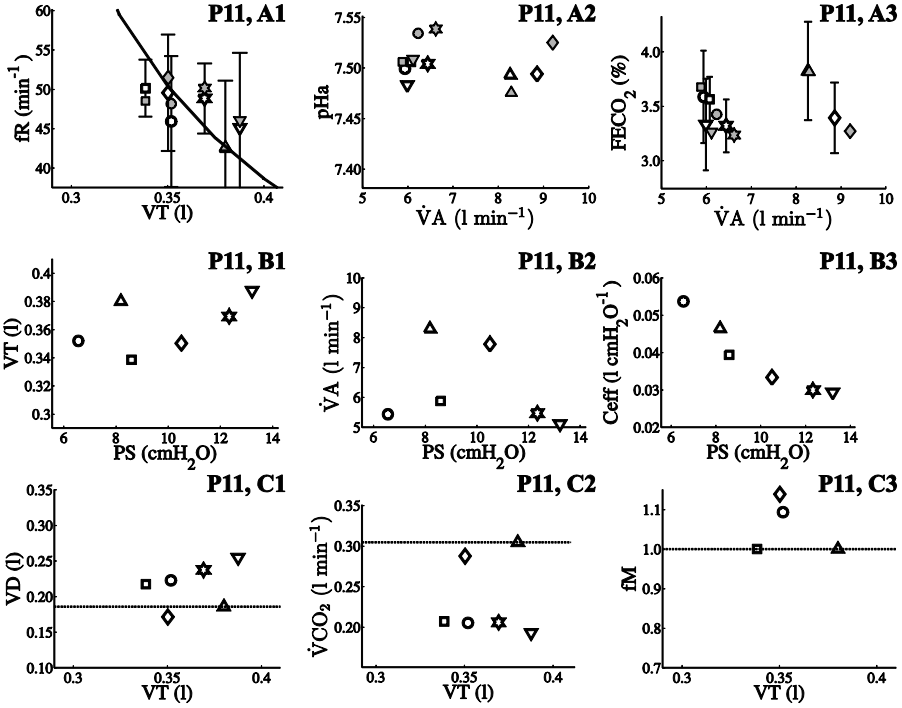

Figure B-11. Measured and model simulated patient response to changes in PS. Patient 11.

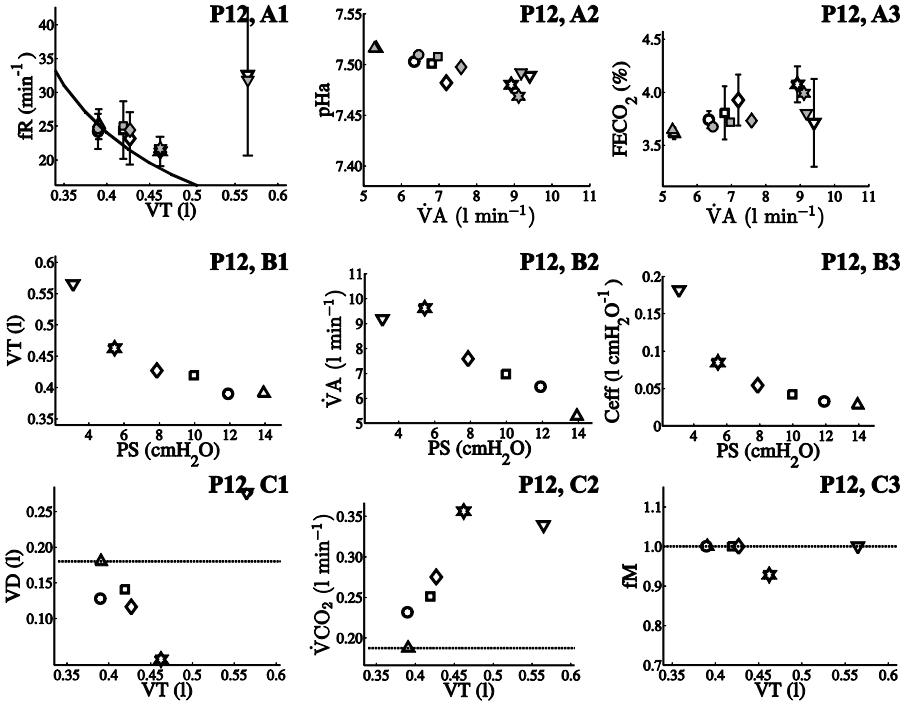

Figure B-12. Measured and model simulated patient response to changes in PS. Patient 12.

Appendix C. List of articles

This thesis is based in three articles:

I. A mathematical model for simulating respiratory control during support ventilation modes. DOI: 10.3182/20140824-6-ZA-1003.01024
II. A mathematical model approach quantifying patients' response to changes in mechanical ventilation: Evaluation in volume support. DOI: 10.1016/j.medengphy.2014.12.006
III. A mathematical model approach quantifying patients' response to changes in mechanical ventilation: Evaluation in pressure support. Article submitted and on review.

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