Computational simulation indicates that moderately high-frequency ventilation can allow safe reduction of tidal volumes and airway pressures in ARDS patients

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Abstract

Background: A recent prospective trial using porcine models of severe acute respiratory distress syndrome (ARDS) indicated that positive-pressure ventilation delivered by a conventional intensive care ventilator at a moderately high frequency allows safe reduction of tidal volume below 6 ml/kg, leading to more protective ventilation. We aimed to explore whether these results would be replicated when implementing similar ventilation strategies in a high-fidelity computational simulator, tuned to match data on the responses of a number of human ARDS patients to different ventilator inputs.

Methods: We evaluated three different strategies for managing the trade-off between increasing respiratory rate and reducing tidal volume while attempting to maintain the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) constant on a computational simulator configured with ARDS patient datasets.

Results: For a fixed sequence of stepwise increases in the respiratory rate, corresponding decreases in tidal volume to keep the alveolar minute ventilation and inspiratory flow constant were calculated according to standard formulae. When applied on the simulator, however, these sequences of ventilator settings failed to maintain $PaCO_2$ adequately in the virtual patients considered. In contrast, an approach based on combining numerical optimisation methods with computational simulation allowed a sequence of tidal volume reductions to be computed for each virtual patient that maintained $PaCO_2$ levels while significantly reducing peak airway pressures and dynamic alveolar strain in all patients.

Conclusions: Our study supports the proposition that moderately high-frequency respiratory rates can allow more protective ventilation of ARDS patients and highlights the potential role of high-fidelity simulators in computing optimised and personalised ventilator settings for individual patients using this approach.

Keywords: Acute respiratory distress syndrome, Positive-pressure ventilation, Ventilator-induced lung injury, Computational simulation

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Background

Acute respiratory distress syndrome (ARDS) is a severe condition that affects around 1 in 10,000 people every year with the mortality rate of 40–50 % [1, 2]. Mechanical ventilation (MV), involving the use of mechanical force to offload respiratory muscles of their work, is a fundamental component of treatment in the intensive care unit (ICU) for patients with ARDS. However, a problematic issue associated with MV is that it exposes patients' lungs to potentially destructive energy applied by the ventilator [3]. Consequently, MV can induce lung injury and can increase the risk of non-pulmonary organ injury/failure, which further adds to morbidity and mortality for ARDS patients [4].

A number of studies have shown that lowering the tidal volume (V_T) can improve mortality rates in ARDS patients. Hickling et al. [5] reported a 60 % decrease in the expected mortality rate among patients with ARDS by lowering V_T. In another trial, Amato et al. [6] investigated changing conventional V_T (12 ml/kg of predicted body weight, PBW) to low V_T and reported a 46 % reduction in mortality. This benefit was also confirmed in the ARDS Network study with mortality decreased by 22 % in the low tidal volume intervention group [7]. However, reducing V_T by itself also leads to worsened partial pressures of arterial oxygen (PaO_2) and carbon dioxide ($PaCO_2$) and arterial pH [8].

An alternative approach to achieve more protective ventilation is high-frequency oscillatory ventilation (HFOV) [9]. In this approach, patients' lungs are not allowed to exhale fully (keeping them partially inflated, which maintains oxygenation), while CO_2 is cleared by moving small volumes of gas in and out of the respiratory system at 3 to 15 Hz (180 to 900 b/min). This process has the potential to minimise the repeated opening and collapsing of lung units that can cause secondary lung damage during mechanical ventilation [10]. Although HFOV is now a widely used lung-protective strategy in the treatment of neonatal and paediatric acute lung injury [11], it cannot be implemented on conventional ventilators, and clinical studies have so far failed to show a significant effect on mortality in adult patients undergoing mechanical ventilation for ARDS [12, 13].

A number of previous studies have also investigated the potential of moderately high-frequency ventilation using standard ventilators [14, 15]. In this approach, respiratory rates (RRs) applied are beyond the limits of traditional mechanical ventilation but below those used in HFOV. A recent prospective study using porcine models ($N = 8$) in which ARDS was induced by pulmonary lavage and injurious ventilation [16] supported the potential of moderately high-frequency ventilation to allow safe reductions in V_T and airway pressures while maintaining stable $PaCO_2$ levels.

In this study, we explore whether the application of a similar approach using a high-fidelity computational simulator tuned to a number of human ARDS patient datasets confirms or refutes the results of this previous animal study. We also investigate a number of different approaches for practically implementing moderately high-frequency ventilation, by considering alternative algorithms for maintaining $PaCO_2$ and reducing alveolar strain.

Methods

Computational simulator

The computational simulator used in this study is a multi-compartmental computational model that uses an iterative, time-sliced, arithmetic technique to simulate integrated respiratory and cardiovascular pathophysiological scenarios [17–19]. The core models in

the simulator have been designed to represent a dynamic in vivo cardiovascular-pulmonary state using a set of mass-conserving equations based on well-established physiological principles. The model simulates a lung comprising conducting airways and 100 alveolar compartments, with each compartment having a corresponding set of parameters accounting for stiffness, threshold opening pressures (TOPs) and extrinsic pressures as well as airway and peri-alveolar vascular resistances. The mathematical principles and equations on which the simulator is based have been detailed in previous studies [20–22], which have also validated the simulator's ability to represent the pulmonary disease states of individual patients with chronic obstructive pulmonary disease and ARDS. A detailed description of the principles and mathematical equations underlying the computational model implemented in our simulator is provided in Additional file 1.

Model matching to ARDS patient data

The model was configured to match data from individual ARDS patients reported by Nirmalan and colleagues [23], which listed arterial and mixed venous blood gas values and cardiac output measurements taken from patients treated for ARDS. The problem of matching the model's outputs to the patient data reported in [23] was formulated as an optimisation problem, where the difference between the simulated model outputs and the data is measured by a cost function. Internal model parameters are then varied by a numerical optimisation algorithm [24] in order to minimise this cost function. The cost function that captures the matching error between the model and the data is defined as:

$$E_{\mathrm{T}} = \sum_{i=1}^{n} E_i^{2} \tag{1}$$

where E_{T} is the total residual error representing the matching accuracy and $E_i = \frac{x_i - x_{id}}{x_{id}}$ is the error for output i, x_i is the value of output i returned by the simulation and x_{id} is the value of the data for that output. The model parameters for each compartment i used for the matching include threshold opening pressure TOP_i, stiffness coefficient S_i and extrinsic pressure $P_{\mathrm{ext},i}$, meaning that a total of 300 model parameters are considered for 100 compartments in the simulator. During the matching process, these parameters are allowed to vary continuously between physiologically realistic upper and lower bounds as defined in Table 1.

Global optimisation algorithms can then be used to find model parameter values that minimise the value of E_{T}, i.e. minimise the difference between the model outputs and the data. The procedure is illustrated in detail in Additional file 1—in each iteration, a set of parameter combinations are sent to the simulator and the outputs from the simulator are evaluated by the optimisation algorithm which then generates the updated parameter values for the next iteration until the condition to get a best

Table 1 Nominal values and allowable ranges for the model parameters

Parameters	Nominal value	Variation ranges
TOP_i (cmH$_2$O)	30	(5, 60)
Stiffness coefficient S_i (cmH$_2$O/ml^2)	0.05	(0.005, 0.5)
Extrinsic pressure $P_{\mathrm{ext},i}$ (cmH$_2$O)	28.8	(−20, 28.8)

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matching is found. In this study, we employed an advanced global optimisation algorithm known as a *genetic algorithm*, a general-purpose, stochastic search and optimisation procedure, based on genetic and evolutionary principles [24]. Full details of the particular optimisation algorithm used in this study and how it was implemented with the model are also provided in Additional file 1.

Strategies for implementing moderately high-frequency ventilation

After matching the model to the patient datasets, three different ventilation strategies were applied and evaluated separately on each of the virtual patients. The primary objective of the ventilation strategies was always to maintain a constant $PaCO_2$ while increasing RR and reducing V_T.

Strategy 1

The first two strategies attempt to calculate appropriate ventilator settings based on simple physiological equations that are widely used in clinical practice. To maintain $PaCO_2$, patients are expected to have constant alveolar minute ventilation, which can be calculated using the following equation [25]:

$$M_V alv = RR \times (V_T - V_D anat) \tag{2}$$

In Eq. (2), $M_V alv$ is the alveolar minute ventilation, RR is the respiratory rate, V_T is the tidal volume and $V_D anat$ is the anatomical dead space. To investigate the effect of higher frequency ventilation, the ventilator rate RR for each of the virtual patients is increased from 16 to 48 b/min in steps of 8 b/min, with each step lasting for 20 min. At each step, the corresponding V_T is reduced according to Eq. (2) above, so as to maintain constant alveolar minute ventilation. $V_D anat$ can be estimated based on the ideal body weight [26]; in this study, we used a value of 160 ml, based on an adult patient with ideal body weight of 70 kg.

Strategy 2

Here, as well as keeping alveolar minute ventilation constant using Eq. (2), the inspiratory flow is also kept constant (this corresponds to the strategy implemented in [16]). This can be achieved in our simulator by using the equation [25]:

$$F_{insp} = \frac{V_T \times RR}{60 DC} \tag{3}$$

where F_{insp} is the inspiratory flow into the lung from the ventilator and DC is the duty cycle (inspiratory time divided by total cycle time). From Eq. (3), by varying DC, F_{insp} can be manipulated since V_T is already determined by Eq. (2). Thus, the difference between strategies 1 and 2 is that DC is set as constant for the first, while for the latter, DC is varied to achieve constant inspiratory flow.

Strategy 3

An alternative approach to computing changes in ventilator settings based on simple physiological equations is to exploit the computational simulator directly. In this approach, we use numerical optimisation to calculate the value of V_T at each increment of RR that will minimise the change in the value of $PaCO_2$. For each value of RR from 16 to 48 b/min at each step, the corresponding values of V_T (denoted by $p_1, p_2,..., p_5$) are selected by an optimisation algorithm between a lower bound of 2.5 ml/kg and an upper bound of 8 ml/

kg. A cost function is defined as the difference between the model-generated values and the initial value of $PaCO_2$. During the optimisation process, the values of p_i are considered as optimisation variables that are systematically varied within the bounded space until the values that minimise the cost function are found. The process is then repeated for all three patient models.

Results

Matching the simulator to ARDS patient datasets

To configure the virtual ARDS patients, three sets of patient data from Nirmalan's study [23] were used, which are classified as mild (patient A, partial pressure of arterial oxygen/ fraction of inspired oxygen (PaO_2/FIO_2) ratio 253.9 mmHg), moderate (patient B, PaO_2/FIO_2 ratio 166.3 mmHg) and severe (patient C, PaO_2/FIO_2 ratio 55.6 mmHg) according to the ARDS Berlin definition [27]. The initial V_T was set at 8 ml/kg (assuming ideal body weight of 70 kg), and RR was set to 12.5 b/min for all three patients. The cardiac output (CO), FiO_2 and haemoglobin (Hb) were configured using the data reported in the reference. Pulmonary vascular resistance (PVR) and compliance used for the model are also reported in Table 2. The model outputs to be matched included PaO_2, partial pressure of oxygen in mixed venous blood (PvO_2), partial pressure of carbon dioxide in the venous blood ($PvCO_2$) and pulmonary shunt fraction. The initial value of $PaCO_2$ was produced by the model at the matched state. An optimisation algorithm was run to minimise the difference between model outputs and the data based on Eq. (1), until a predefined termination criterion was reached. The model-fitting results are reported in Table 2; this shows that close matches to each of the three patient datasets were achieved by the simulator.

Effectiveness of the three ventilation strategies

The ventilation settings used for each strategy are reported in Table 3 and are also shown in Fig. 1. For strategies 1 and 2, the same settings for V_T are applied to each patient; see Fig. 1a. For strategy 3, the optimal values of V_T are computed for each patient using numerical optimisation; see Fig. 1b. Figure 1c shows the same pattern of RR applied for all strategies, and the variations of DC are shown in Fig. 1d. The
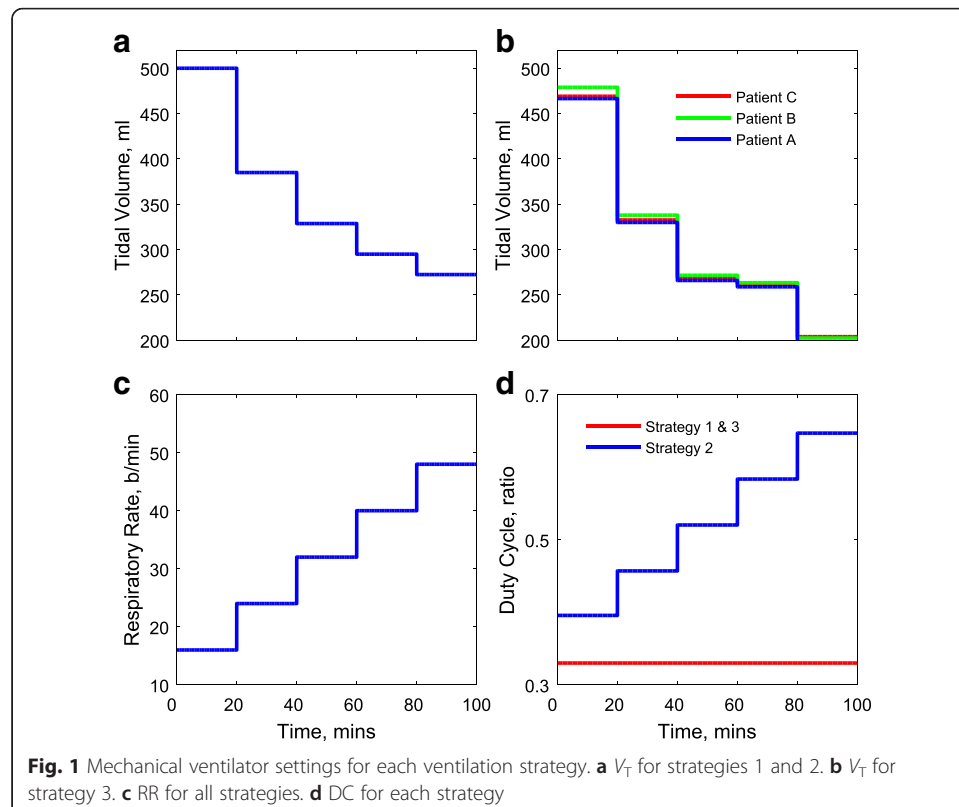
Table 2 Model fitting for three ARDS patients

	Patient A		Patient B		Patient C	
CO (l/min)	13.0		10.1		3.9	
FIO_2	0.8		1		1	
Hb (g/l)	112		79		98	
PVR (dyn s cm^{-5})	152.0		152.1		151.9	
C_{dyn} (ml/mbar)	37		31		33	
DC (ratio)	0.33		0.33		0.33	
RR (b/min)	12.5		12.5		12.5	
	Data	Model	Data	Model	Data	Model
PaO_2 (mmHg)	201	203.1	165.75	166.29	56.32	55.59
PvO_2 (mmHg)	45.83	47.68	42	41.51	24.83	25.66
$PvCO_2$ (mmHg)	46.73	43.34	43.5	43.61	39.3	39.79
Shunt (% of CO)	30.0	30.8	33.5	34.7	34.7	35.21

Table 3 Ventilation settings for strategies 1 and 2

RR (b/min)	16	24	32	40	48
V_T (ml)	497.5	385	328.75	295	272.5
$V_D$anat (ml)	160	160	160	160	160
$M_V$alv (ml/min)	5400	5400	5400	5400	5400
DC (ratio) (strategy 1)	0.33	0.33	0.33	0.33	0.33
DC (ratio) (strategy 2)	0.40	0.46	0.52	0.58	0.65
F_{insp} (ml/s) (strategy 1)	404.04	466.67	531.31	595.96	660.61
F_{insp} (ml/s) (strategy 2)	337	337	337	337	337

corresponding changes of the P/F ratio, $PaCO_2$, peak alveolar pressure (P_{alv}, calculated from the 25 % of alveoli with highest pressures), dynamic compliance (C_{dyn}) and the volume of the lung at the end of inhalation and exhalation (V_{lung}) for each patient are shown in Figs. 2, 3 and 4. For all patients, strategies 1 and 2 led to significant changes in $PaCO_2$, whereas strategy 3 kept the value of $PaCO_2$ almost constant for all combinations of V_T and RR. The changes in $PaCO_2$ observed for strategies 1 and 2 are accompanied by large increases in the P/F ratio (due to alveolar recruitment arising from increases in P_{alv})—only strategy 3 showed a consistent reduction in P_{alv} as RR increased, i.e. only strategy 3 implemented a more *protective* ventilation strategy. The potential of moderately high-frequency ventilation to deliver more protective ventilation is further supported by Fig. 5, where dynamic strain (V_T/FRC, ratio) can be seen to decrease most significantly in all three simulated patients as RR is increased using strategy 3.
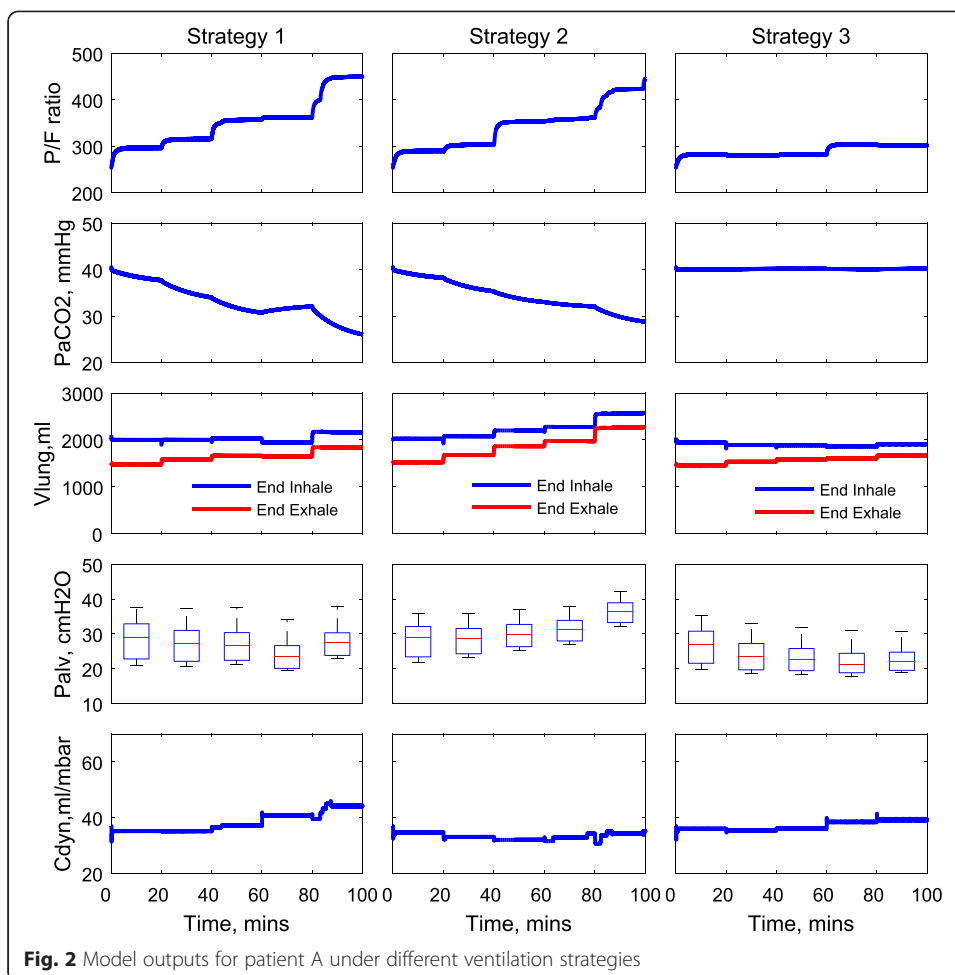

Fig. 1 Mechanical ventilator settings for each ventilation strategy. **a** V_T for strategies 1 and 2. **b** V_T for strategy 3. **c** RR for all strategies. **d** DC for each strategy

Fig. 2 Model outputs for patient A under different ventilation strategies

Discussion

Why do strategies 1 and 2 result in large changes in $PaCO_2$ when they are predicated on maintaining constant alveolar minute ventilation and inspiratory flow? The answer is provided by Fig. 6, which plots the relationship between the total dead space (physiological dead space, $V_D phys$) calculated in the simulation model and V_T for each virtual patient. As shown, as RR increases, the value of $V_D phys$ is not constant, as assumed in Eqs. (2) and (3) using $V_D anat$ (on which strategies 1 and 2 are based), but is strongly proportional to V_T. It may also be observed that the ratio $V_D phys/V_T$ is similar through the spectrum of ARDS severity. Interestingly, this relationship has previously been shown experimentally in the context of high-frequency ventilation [28]. Thus, the simple formulae on which strategies 1 and 2 are based do not correctly compute the required changes in V_T and RR to keep alveolar minute ventilation constant with either constant or variable inspiratory flow.
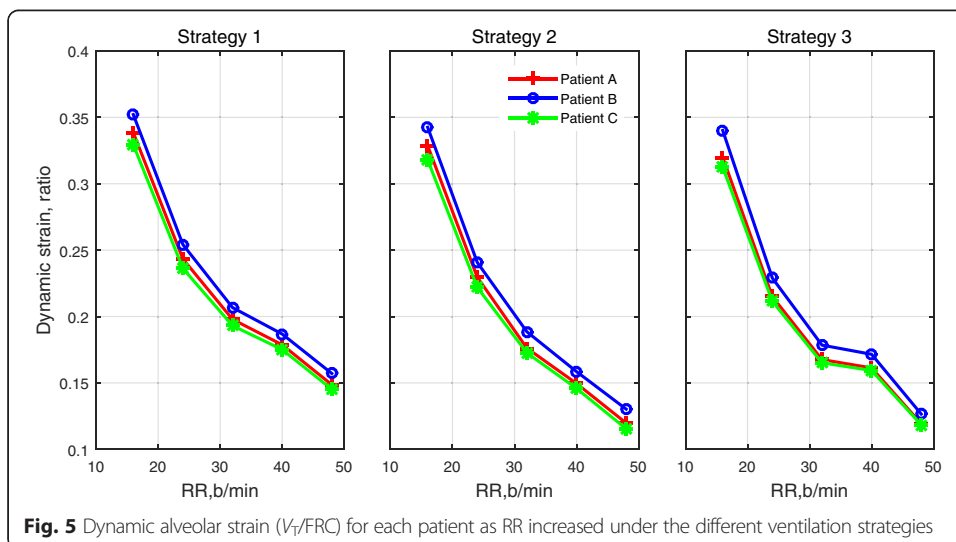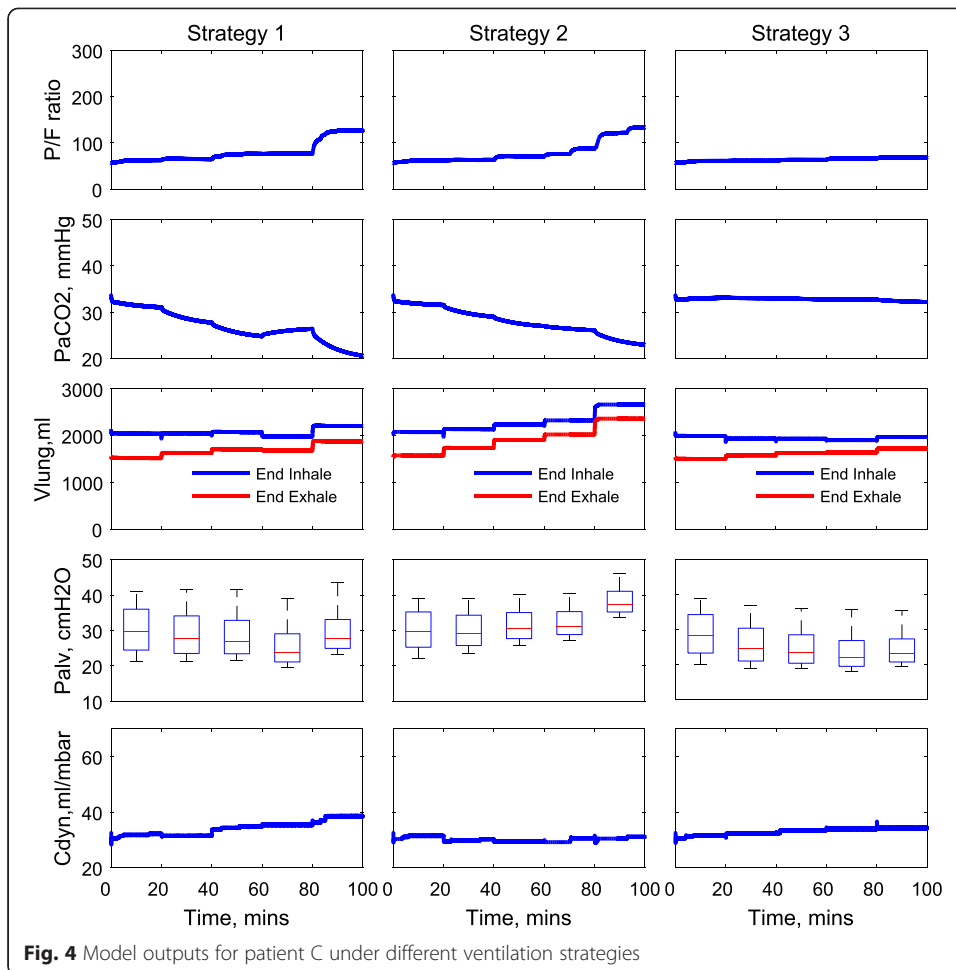
A test was performed using the model that calculated $V_D phys$ instead of $V_D anat$ during each step to estimate which V_T should be applied in the next change of RR to maintain $M_V alv$ based on Eq.(2). The simulation results for patient C using strategy 1 with the calculated $V_D phys$ are shown in Fig. 7. It can be seen that although $PaCO_2$ was not constant, it remained within an acceptably narrow range, which is significantly improved compared with the results in Fig. 4. In practice, therefore, if a device could
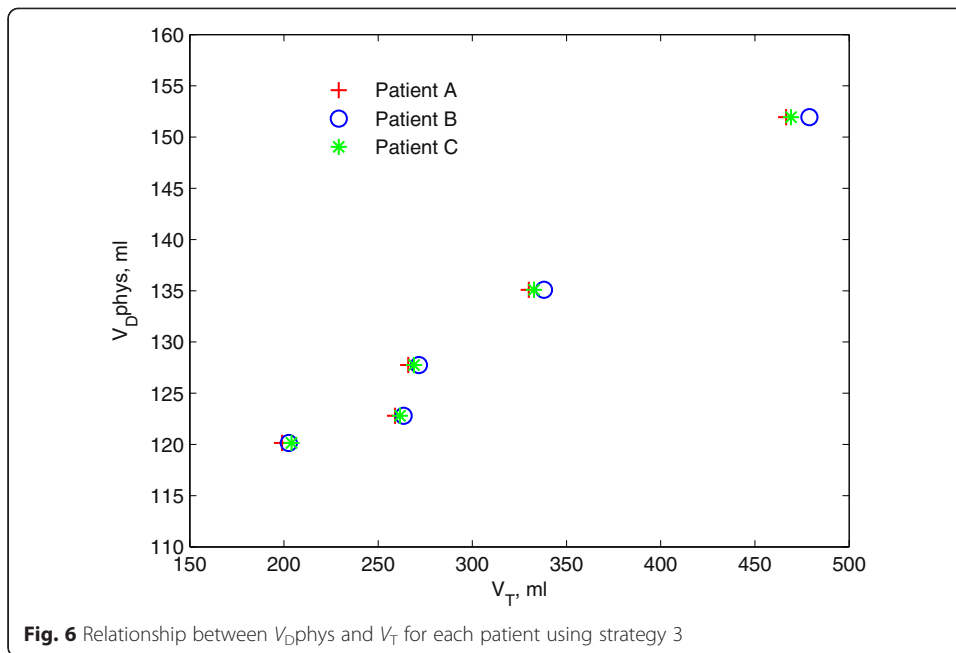
Fig. 3 Model outputs for patient B under different ventilation strategies
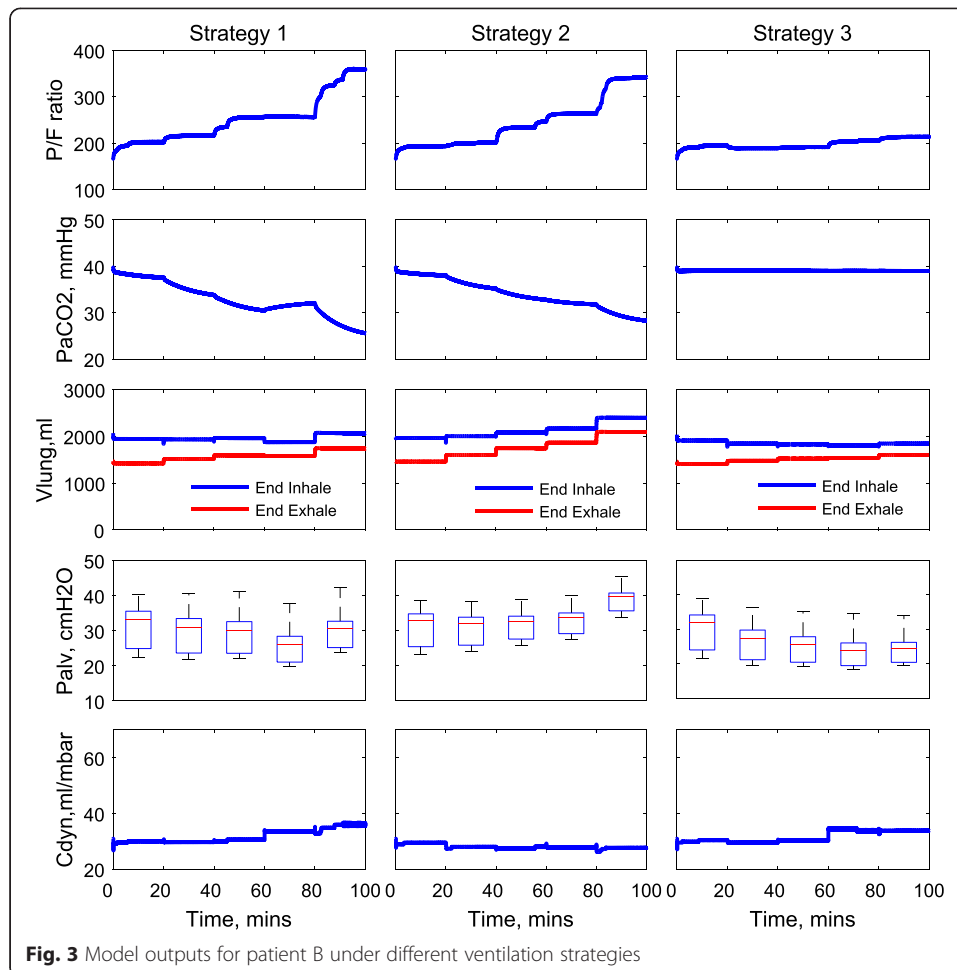
provide a measurement of $V_D$phys in a sufficiently short time, our results indicate that $PaCO_2$ could be well controlled using this approach.
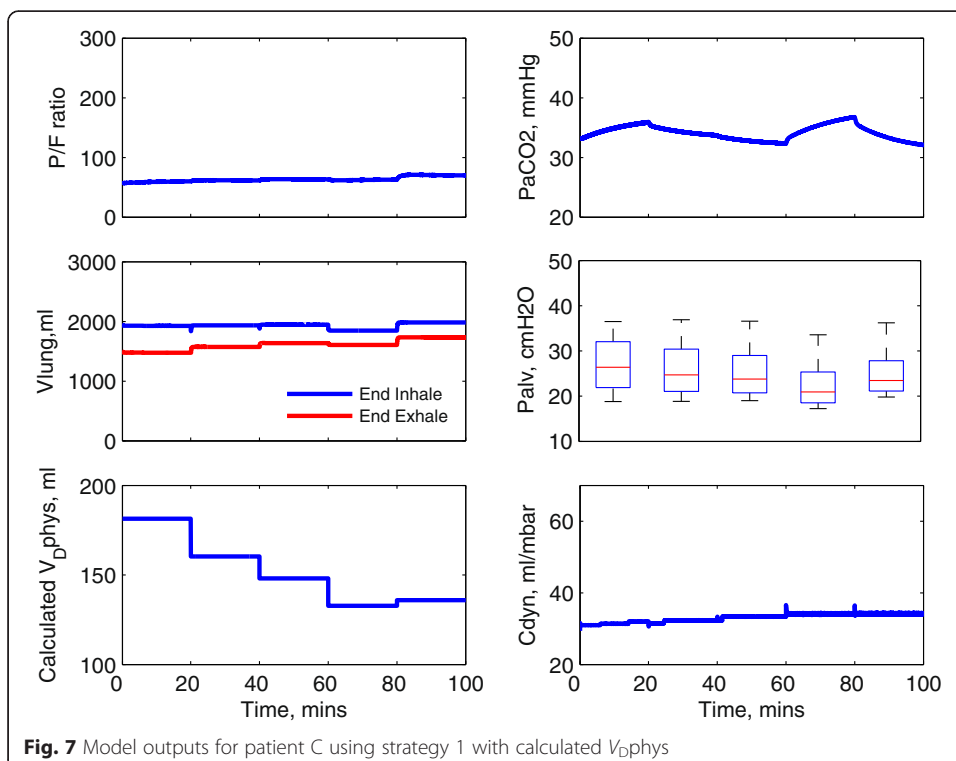
The benefits of a normal or only slightly elevated level of $PaCO_2$ in critically ill patients are well recognised. It is, however, difficult and sometimes impossible to achieve this in a patient with ARDS without increasing the risk of alveolar injury. The concept of permissive hypercapnia is now an accepted management strategy for the critically ill lung. The rationale behind this approach is primarily to minimise lung strain, which could otherwise be worsened by strenuous ventilatory strategies aimed at keeping $PaCO_2$ within normal physiological limits. However, in a very severe lung disease, the rise in $PaCO_2$ is sometimes difficult to control using conventional protective ventilation strategies. Extracorporeal CO_2 removal devices have been used in clinical practice for a few years now, but they bring potentially dangerous side effects [29]. The efficacy of these devices in allowing ultra-protective ventilation strategies, with tidal volumes and pressures comparable to those used in our model simulation, is being tested at present in the SUPERNOVA trial [30].

The benefit of the moderately high-frequency ventilation strategies we tested in this model is that they allow the maintenance of a normal level of $PaCO_2$ while seeming to have the potential for decreasing the risk of lung injury and, in some cases, while recruiting the lung. The problem of improving lung protection in ARDS is obviously an

Fig. 4 Model outputs for patient C under different ventilation strategies

Fig. 5 Dynamic alveolar strain (V_T/FRC) for each patient as RR increased under the different ventilation strategies

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Fig. 6 Relationship between $V_D$phys and V_T for each patient using strategy 3

extremely complex and multifaceted one and involves consideration of multiple factors beyond mechanical pressure limits. Nonetheless, our results indicate that moderately high-frequency ventilation could represent a beneficial ventilation strategy in ARDS patients with reduced respiratory system compliance. An interesting question for future investigation is to determine the potential for reducing driving pressure using this

Fig. 7 Model outputs for patient C using strategy 1 with calculated $V_D$phys

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strategy, since a recent retrospective analysis of nine randomised trials indicated that driving pressure was the variable most strongly associated with survival [31]. Our study has a number of limitations, principally the small number of "virtual" patients evaluated and the lack of prospective validation in clinical trials. We note, however, that our findings confirm and help to explain the results of a previous study using animal models that investigated very similar changes in ventilator settings [16].

Conclusions

By using a high-fidelity computational simulator, a more protective ventilation strategy consisting of progressive reductions in V_T with simultaneous increases in RR could be developed for a number of different virtual ARDS patients, covering the spectrum from mild to severe presentations of the disease. This strategy allowed changes in $PaCO_2$ to be kept within an acceptable range in each case, thus confirming the results reported on a cohort of porcine models in [16], which showed that moderately high-frequency ventilation could allow safe reductions in the levels of V_T. Attempts to compute appropriate values for the decrements in V_T required to compensate for increments in RR using simple mathematical formulae were not successful, due to the fact that dead space varies significantly with changes in V_T. Our results demonstrate the importance of using advanced simulation models in order to correctly represent the complex dynamics of ventilator-lung interactions and highlight the potential of such models to refine or replace animal trials in this area.

Additional file

Additional file 1: Simulation model description and optimisation algorithm description.

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