

EDITORIAL

Simulation to minimise patient self-inflicted lung injury: are we almost there?

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Summary

Computational modelling has been used to enlighten pathophysiological issues in patients with acute respiratory distress syndrome (ARDS) using a sophisticated, integrated cardiopulmonary model. COVID-19 ARDS is a pathophysiologically distinct entity characterised by dissociation between impairment in gas exchange and respiratory system mechanics, especially in the early stages of ARDS. Weaver and colleagues used computational modelling to elucidate factors contributing to generation of patient self-inflicted lung injury, and evaluated the effects of various spontaneous respiratory efforts with different oxygenation and ventilatory support modes. Their findings indicate that mechanical forces generated in the lung parenchyma are only counterbalanced when the respiratory support mode reduces the intensity of respiratory efforts.

Keywords: ARDS; computational modelling; COVID-19; lung injury; patient self-inflicted lung injury; simulation

In a recent issue of the British Journal of Anaesthesia, Weaver and colleagues¹ used sophisticated computational modelling to elucidate factors contributing to the generation of patient self-inflicted lung injury (P-SILI). They evaluated the effects of different oxygenation and ventilatory support modes which induced variable (in number and strength) spontaneous respiratory efforts. The authors, who are experienced in simulation,^{2–6} used data concerning COVID-19 acute respiratory distress syndrome (ARDS) pathophysiology to configure a virtual cohort of 120 patients with various combinations of poorly aerated lung tissue, and lung tissue affected by microthrombi.¹ Simulation has been defined as a ‘technique to replace or amplify real experiences with guided experiences that evoke or replicate substantial aspects of the real world in a fully interactive manner’.⁷ It is rather a technique, not technology, referring to a device, the ‘simulator’, that represents a simulated patient (or a specific body part or structure) that interacts appropriately with the actions taken by the simulation participant. Healthcare

simulators are analogous to the ones used in commercial aviation in terms of complexity and reliability demands. They were developed in response to the need of patient safety assurance, representing a complex real-world process with sufficient fidelity to facilitate learning, avoiding the inherent risks that might arise in real-life practice.^{7,8} Computational modelling has several applications in critical illness. Firstly, it provides an understanding of pathophysiological mechanisms and responses.² Complex system dynamics can be modelled based on clinical patient data, introducing an alternative to *in vivo* and *in vitro* trials. Secondly, simulations provide powerful teaching materials.⁹ Since Resusci-Anne (Laerdal, Stavanger, Norway), one of the first healthcare simulation models, great advances have been made in the complexity of the teaching models integrating lung and circulation physiology with the mechanical properties of ventilators to model patient–ventilator interactions.⁸ Thirdly, simulation can help clinicians predict patient responses to planned therapies. Computational modelling has mainly been used to evaluate the pharmacokinetic/pharmacodynamic (PK/PD) properties of

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experimental drugs before they are launched in the clinical practice. In the drug industry, simulation studies, using population PK models, evaluate the probability of drug target attainment and recommend an optimal dosing regimen. They provide information on the optimal drug dosing according to PK/PD data, which are then validated in clinical practice through phase 3 studies.^{10,11}

Computational modelling has also been used to enlighten pathophysiological issues in ARDS patients using a highly sophisticated, integrated cardiopulmonary model.³ This multi-compartmental cardiopulmonary simulator, comprising of 100 alveolar units, has been used to simulate ARDS lung pathology and the responses to different interventions such as recruitment manoeuvres, PEEP effects on oxygen delivery, and increased breath rates.^{2,4–6} Through simulation studies, efforts are made to elucidate the complex alveolar tissue–mechanical power interaction, with the aim to understand the risk of Ventilator Induced Lung Injury (VILI).¹² Hamlington and colleagues¹³ proposed that the product of volutrauma and atelectrauma predicts VILI better than the additive effects of each component, whereas Bates and colleagues¹⁴ evaluated which form of ‘trauma’, volume or atelectasis, is worse for VILI. They found that both volume and pressure are reasonable targets as long as they are kept under certain thresholds.^{13,14} The results are replicated from large clinical data suggesting that lung-protective ventilation strategies should primarily target driving pressure rather than tidal volume when airway pressures are kept low.¹⁵ Mathematical models are also evaluated for the identification of variables that may injure the lungs or even the diaphragm.¹⁶ These studies would be unethical in a clinical setting; thus simulation has a lot to offer. Moreover, simulation has refined knowledge concerning new ventilation modes and their clinical application, such as elimination of patient–ventilator asynchrony.¹⁷

A new pathophysiologically distinct type of ARDS was identified during the COVID-19 pandemic, characterised by a significant dissociation between impairment in gas exchange and respiratory system mechanics (compliance of the respiratory system [CRS]), especially in the early stages of ARDS.¹⁸ Extensive ground glass opacification (absence of dense consolidation, in dependent lung regions) and extensive effects on the pulmonary capillary bed (thrombosis, blunted hypoxic pulmonary vasoconstriction reflexes) are some of the underlying pathophysiological mechanisms offered to explain this dissociation.^{18–21} A new term, CARDS, was proposed to characterise COVID-19 ARDS, intended to characterise not only the diversity of implicated mechanisms, but also to propose a more conservative therapeutic approach, especially concerning PEEP levels.^{18,22,23} Optimal tracheal intubation time has been a matter of discussion as well, especially with the perspective of P-SILI induced by increased respiratory effort. Delayed intubation has been shown to affect respiratory system mechanics adversely.²⁴

Simulation is invaluable when addressing issues relating to management of mass casualties. With this perspective, Weaver and colleagues¹ evaluated the underlying pathophysiology in COVID-19 ARDS and proposed optimal respiratory management to minimise secondary lung injury. Their study broadens the areas of computational modelling focus to include the concept of P-SILI. They simulated COVID-19 ARDS and quantified responses to different ventilatory modalities with a focus on mechanical forces generated in the pulmonary parenchyma under various degrees of respiratory effort and oxygenation support modalities. Measurements of respiratory

system and lung compliance, lung stress and strain, and pleural and transpulmonary pressure swings as indices of lung injury were obtained in each simulated patient with different respiratory support modalities (conventional oxygen therapy [COT], continuous positive airway pressure [CPAP], high flow nasal oxygen treatment [HFNOT], noninvasive ventilation [NIV], and invasive mechanical ventilation) and various levels of respiratory effort. To quantify respiratory effort, they applied four combinations of ventilatory frequency (30, 27, 24, 21 bpm) and negative respiratory muscle pressure (26, 23, 20, 17 cm H₂O).¹ One of the strengths of the study is that the simulation experiments were based on all the currently available knowledge regarding COVID-19 ARDS pathophysiological mechanisms. COVID-19 ARDS combines severe hypoxaemia with preserved lung mechanics, at least in the early stages of the disease.¹⁸ The simulated cohort of patients included ‘lungs’ with differences in the distribution of compliance (using different combinations of alveolar collapse, dead space, and alveolar gas-trapping).

Evaluation of different ventilatory modalities and their effects on lung mechanics in the same patient is the major strength of the study. The results clearly emphasise the importance of respiratory effort in the amplification of lung injury in ARDS. The higher the pleural pressure swings during spontaneous breathing, the greater the stress and strain produced in the lung parenchyma. Simulation also indicated that although the different modalities of respiratory support (CPAP, HFNOT, NIV) can effectively improve oxygenation status (depicted by increases in both P_{aO_2} , and SaO_2), the risk of further aggravating lung injury (in an already diseased lung tissue) was reduced only when the respiratory support could decrease the amplitude of the respiratory effort. A reduction in respiratory effort equivalent to a reduction in pleural pressure swings by 12 cm H₂O was needed to decrease total lung strain. Yet, only for HFNOT could the stress and strain values be reduced below baseline values, although improvement in oxygenation was comparable among the three treatment modalities.

Weaver and colleagues show that when spontaneous respiratory effort ceased, protective mechanical ventilation settings (tidal volume of 7 ml kg⁻¹, PEEP of 5 cm H₂O, ventilatory frequency of 20 bpm) reduced all measured indices of lung damage. Stress and strain only increased with increases in PEEP. Similarly, increases in airway pressure to overcome increased threshold of airway pressure resulted in increased lung stress and strain. Certainly, invasive mechanical ventilation is a reasonable approach, but it should not be offered to every COVID-19 patient with ARDS. Mechanical ventilation is accompanied by many complications, and ventilator-associated pneumonia has been increasingly identified in the COVID-19 era.²⁵ Thus, clear criteria for tracheal intubation should be followed, although the surge of patients with COVID-19 ARDS greatly impacted intubation timing decisions during the pandemic.²⁴

Weaver and colleagues clearly highlight the limitations of their experiments. Their results are only based on computational modelling without physiological validation, which limits the generalisability of the findings. Yet, modelling for managing mechanical ventilation is an emerging approach to understanding patient–ventilator interactions with newer ventilation modes, such as proportional assist ventilation, in clinical practice.²⁶ Simulation can guide the design (target population, patient characteristics, comorbidities) of clinical trials, as many variables or patient characteristics are tested in simulation studies, which could not be evaluated in real-life

studies.²⁷ Simulation studies are suggestive, and effective feedback from clinical trials is needed. Refining the integrated cardiopulmonary simulation models increases the reliability of information on oxygen delivery and consumption. The results of the present study suggest guidance for management during the COVID-19 pandemic, and provide a rationale for early intubation in patients with COVID-19 ARDS in cases in which ventilatory support cannot ameliorate increased respiratory efforts. P-SILI is evident in laboratory studies, yet not well identified clinically. Experimental data have shown that in acute lung injury, spontaneous breathing can provoke increased volumetric strain and heterogeneity in lung units, a finding that was not observed in animals managed with mechanical ventilation and low tidal volumes.²⁸ These lung regions may be a source of inflammation and alveolar disruption²⁹ that could possibly trigger secondary lung injury in spontaneously breathing patients with COVID-19 ARDS. Yet there is currently no prospective trial to provide conclusive evidence for P-SILI. The study by Weaver and colleagues provides a basis to design further studies to evaluate the effects of respiratory effort on P-SILI.³⁰

Simulation augments our understanding of the pathophysiological consequences of various conditions and treatments. As with every modelling approach, a critical issue is the predictive validity of the model so that it correctly depicts the clinical dynamics of a process. Knowledge of all mechanisms underlying the pathology of a disease, especially of a novel disease such as COVID-19, is necessarily limited, so insights from simulation studies are welcomed as a guide for refined clinical research.

Declarations of interest

The authors declare no conflicts of interest.

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