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LABORATORY INVESTIGATION

Optimising respiratory support for early COVID-19 pneumonia: a computational modelling study

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Abstract

Background: Optimal respiratory support in early COVID-19 pneumonia is controversial and remains unclear. Using computational modelling, we examined whether lung injury might be exacerbated in early COVID-19 by assessing the impact of conventional oxygen therapy (COT), high-flow nasal oxygen therapy (HFNOT), continuous positive airway pressure (CPAP), and noninvasive ventilation (NIV).

Methods: Using an established multi-compartmental cardiopulmonary simulator, we first modelled COT at a fixed FiO_2 (0.6) with elevated respiratory effort for 30 min in 120 spontaneously breathing patients, before initiating HFNOT, CPAP, or NIV. Respiratory effort was then reduced progressively over 30-min intervals. Oxygenation, respiratory effort, and lung stress/strain were quantified. Lung-protective mechanical ventilation was also simulated in the same cohort.

Results: HFNOT, CPAP, and NIV improved oxygenation compared with conventional therapy, but also initially increased total lung stress and strain. Improved oxygenation with CPAP reduced respiratory effort but lung stress/strain remained elevated for CPAP >5 cm H_2O. With reduced respiratory effort, HFNOT maintained better oxygenation and reduced total lung stress, with no increase in total lung strain. Compared with 10 cm H_2O PEEP, 4 cm H_2O PEEP in NIV reduced total lung stress, but high total lung strain persisted even with less respiratory effort. Lung-protective mechanical ventilation improved oxygenation while minimising lung injury.

Conclusions: The failure of noninvasive ventilatory support to reduce respiratory effort may exacerbate pulmonary injury in patients with early COVID-19 pneumonia. HFNOT reduces lung strain and achieves similar oxygenation to CPAP/NIV. Invasive mechanical ventilation may be less injurious than noninvasive support in patients with high respiratory effort.

Keywords: acute respiratory failure; computational modelling; COVID-19; mechanical ventilation; noninvasive respiratory support; patient self-inflicted lung injury

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Editor's key points

- The authors modelled how different modes of respiratory support may promote lung injury in patients with early COVID-19.
- Unless respiratory effort is reduced by noninvasive respiratory support, lung injury could occur despite improved oxygenation.
- Lung-protective mechanical ventilation improved oxygenation and reduced lung injury.
- The results of this computational modelling mirror and support recent clinical trial findings in COVID-19.

An increasing proportion of patients with acute hypoxaemic respiratory failure caused by COVID-19 pneumonia are initially treated using noninvasive respiratory support. Aside from conventional oxygen therapy (COT), high-flow nasal oxygen therapy (HFNOT), continuous positive airway pressure (CPAP), and noninvasive ventilation (NIV) are all widely used, in the hope of improving oxygenation and avoiding the complications of tracheal intubation and mechanical ventilation.[1] Over the course of the pandemic, few studies have been able to compare directly the effectiveness of different types of noninvasive respiratory support in COVID-19.[2–4] In a recent study of 114 patients with COVID-19 on noninvasive respiratory support,[5] total lung strain was the variable most strongly associated with success or failure (intubation), but in general, there is a lack of data on the potential effects of different types of respiratory support on different indicators of lung injury. Debate is also ongoing as to whether early (pre-emptive) intubation is warranted to reduce the risk of patient self-inflicted lung injury (P-SILI) arising from high respiratory effort during noninvasive respiratory support.[6,7]

To investigate these issues, we hypothesised a conceptual model (Fig 1) in which patients with COVID-19 who initially present with acute hypoxaemia and high respiratory effort benefit from different modes of respiratory support that improve oxygenation but potentially exacerbate lung stress and strain. An optimal mode of ventilatory support would improve oxygenation while reducing respiratory effort to minimise total lung stress, strain, and injury. To test this hypothesis, we adapted a computational simulator of cardiopulmonary pathophysiology to quantify oxygenation, respiratory effort, and mechanical forces that could lead to lung injury after HFNOT, CPAP, and NIV therapy in patients with early-stage COVID-19 pneumonia.

Methods

Study design

This computational modelling study used a multicompartmental cardiopulmonary simulator which has been used to examine both mechanically ventilated[8] and spontaneously breathing[9] patients with COVID-19 acute respiratory failure. The simulator includes 100 alveolar compartments that have independently configurable mechanical properties, allowing for varying levels of collapse, stiffening, disruption of gas exchange, pulmonary vasoconstriction and vasodilation, and airway obstruction. The model represents varying levels of alveolar collapse, ventilation–perfusion mismatch, physiological shunt and dead space, and alveolar gas trapping (see Supplementary material for further detail).

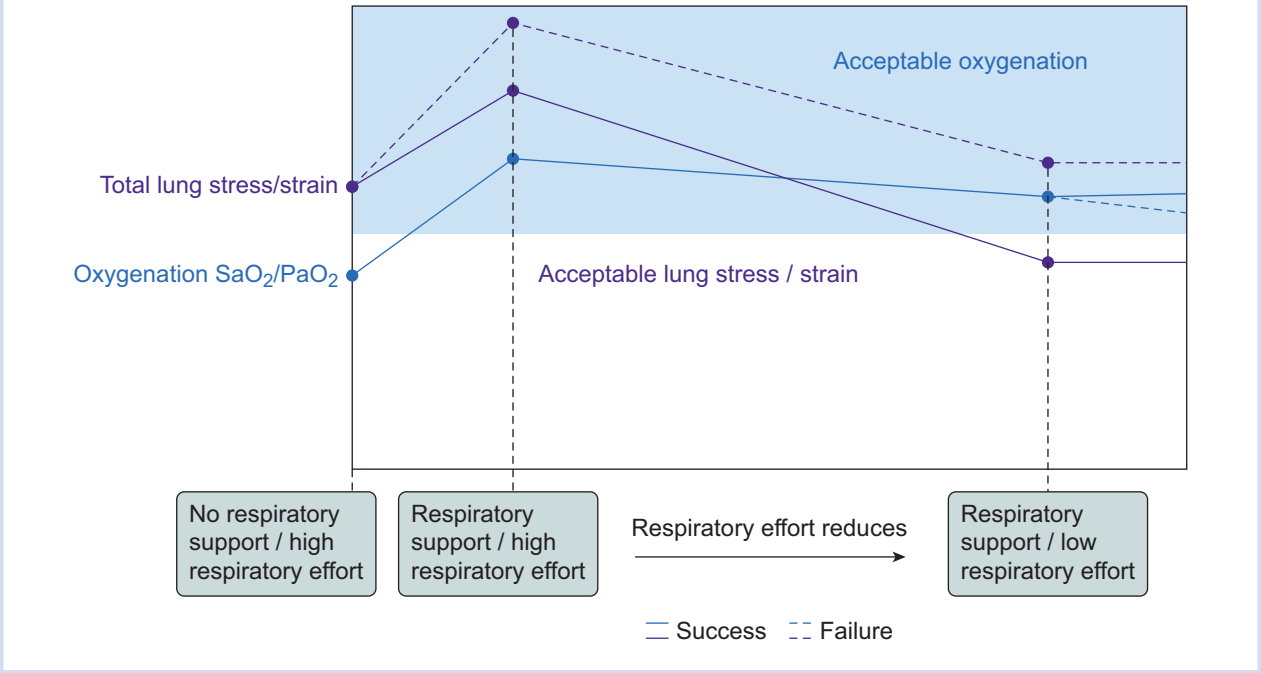

Fig 1. Conceptual model for the application of respiratory support in COVID-19. Solid lines indicate a 'success' case – reduction in respiratory effort enabled by the support is sufficient to reduce stress and strain on the lung to acceptable levels. Dotted lines indicate a 'failure' case, where reduction of respiratory effort fails to reduce stress and strain on the lung to acceptable levels, patient self-inflicted lung injury (P-SILI) accumulates, and oxygenation continues to deteriorate.

Simulated patient cohort

We generated a cohort of virtual patients displaying the particular characteristics of early-stage COVID-19 pneumonia. Following the data of Coppola and colleagues,[5] lung gas volumes and compliance were set to be relatively well preserved by allowing levels of non-aerated and poorly aerated tissue to vary within the ranges 6–13% and 18–22% of the total lung volume, respectively. Alveolar collapse was implemented by increasing parameters representing the extrinsic pressures, threshold opening pressures (TOPs), and threshold closing pressures (TCPs) of the affected alveolar compartments. To determine the TOP distribution for the collapsed alveolar compartments in each patient, a normally distributed range of values was generated with a mean of 28.9 cm H_2O and a standard deviation (SD) of 10.3 cm H_2O, based on the data of Crotti and colleagues.[10] These values were then randomly sampled for each patient to generate a distribution with a mean in the range of 25–30 cm H_2O. The TCP distribution was calculated in a similar manner to generate a distribution for each patient with a mean in the range of 4–6 cm H_2O.[10] Poorly aerated alveoli attributed to the effects of pneumonia were modelled by disrupting gas exchange in the affected compartments. Hyperperfusion of gasless tissues[11] was incorporated by decreasing the vascular resistance of the collapsed compartments by 80%, causing vasodilation. Disruption of hypoxic vasoconstriction (HPV) seen in COVID-19 was included, and the presence of thrombotic complications caused by microthrombi was represented by increasing vascular resistance by a factor of 5 in 14–16% of the remaining compartments.[11] The virtual cohort of 120 patients was generated by taking all possible combinations of the different levels of non-aerated tissue, poorly aerated tissue, and tissue affected by microthrombi within the ranges described above. Details of the pathophysiological characteristics of the virtual patient cohort on COT are shown in Table 1 (first column).

Simulation of respiratory support

Spontaneous breathing on COT (FiO_2=0.6) was simulated as described previously.[9] Respiratory support was modelled by adding additional positive pressures delivering a set FiO_2 to the patient's spontaneous breathing profile during both inspiration and expiration. CPAP was simulated by providing a constant positive pressure of 5, 10, or 15 cm H_2O throughout the breathing cycle delivering an FiO_2 of 0.6.[4,5] NIV was modelled by providing different inspiratory and expiratory support pressures, while also delivering an FiO_2 of 0.6. The inspiratory support pressure was set at 12 cm H_2O whereas the expiratory support pressure was set to 4 or 10 cm H_2O to represent low and high PEEP settings, respectively. HFNOT was modelled as supplying pure oxygen (FiO_2=1) at a rate of 50 L min^{-1}, equivalent to providing a constant pressure of 3 cm H_2O throughout the expiratory cycle.[12] To represent the high flow, the conal mixing function within the simulator was switched on.

The protocol for each patient simulation was as follows:

- COT is simulated with an FiO_2 of 0.6 and an elevated respiratory effort (RE1: respiratory rate RR=30 bpm, peak muscular pressure P_{mus}=−26 cm H_2O) for 30 min to ensure all variables are in steady-state.
- HFNOT, CPAP, or NIV is initiated.
- Respiratory effort is then progressively reduced over 30-min intervals in four steps from RE1 to RE2 (RR=27 bpm, P_{mus}=−23 cm H_2O), RE3 (RR=24 bpm, P_{mus}=−20 cm H_2O), and RE4 (RR=21 bpm, P_{mus}=−17 cm H_2O).

Measures of oxygenation, stress, strain, and other indicators of lung injury are calculated as described in the Supplementary material.

Statistical analysis

Measurements are reported as mean (SD) over the 120 patients. Statistical analysis was not performed owing to the purely deterministic nature of the simulations.

Results

Noninvasive respiratory support

Continuous positive airway pressure

CPAP (5 cm H_2O) delivering an FiO_2 of 0.6 increased SaO_2, with >10 cm H_2O CPAP further improving oxygenation (Fig 2;

Table 1 Effect of applying different levels of CPAP. CPAP values are compared with the baseline case of a patient receiving COT and breathing with high respiratory effort (RE1). Respiratory effort decreases progressively from RE1 to RE4. Red squares indicate increases in indices of lung injury >5%, green squares indicate reductions in indices of lung injury >5%, orange squares indicate a change of <5%. COT, conventional oxygen therapy; CPAP, continuous positive airway pressure.

	COT	CPAP=5 cm H_2O				CPAP=10 cm H_2O				CPAP=15 cm H_2O			
	RE1	RE1	RE2	RE3	RE4	RE1	RE2	RE3	RE4	RE1	RE2	RE3	RE4
PEEP (cm H_2O)	0.00	5.00	5.00	5.00	5.00	10.00	10.00	10.00	10.00	15.00	15.00	15.00	15.00
Respiratory rate (bpm)	30.00	30.00	27.00	24.00	21.00	30.00	27.00	24.00	21.00	30.00	27.00	24.00	21.00
Muscle pressure (cm H_2O)	−26.00	−26.00	−23.00	−20.00	−17.00	−26.00	−23.00	−20.00	−17.00	−26.00	−23.00	−20.00	−17.00
SaO_2 (%)	92.1 (1.9)	93.0 (1.8)	92.9 (1.8)	92.8 (1.8)	92.4 (1.7)	95.7 (1.4)	95.7 (1.4)	95.6 (1.4)	95.4 (1.4)	97.2 (0.7)	97.1 (0.7)	97.0 (0.7)	96.8 (0.7)
PaO_2 (kPa)	8.28 (0.80)	8.65 (0.85)	8.67 (0.85)	8.70 (0.83)	8.85 (0.69)	10.46 (1.3)	10.45 (1.28)	10.44 (1.25)	10.70 (1.14)	12.01 (1.08)	11.94 (1.05)	11.87 (1.02)	12.10 (0.93)
Shunt (%)	32.8 (3.1)	31.6 (3.2)	31.6 (3.2)	31.6 (3.2)	32.2 (2.9)	26.3 (2.9)	26.4 (2.9)	26.4 (2.9)	26.5 (2.9)	23.1 (1.7)	23.1 (1.7)	23.2 (1.7)	23.3 (1.7)
$PaCO_2$ (kPa)	3.33 (0.26)	3.54 (0.16)	3.95 (0.17)	4.52 (0.18)	5.36 (0.24)	3.47 (0.13)	3.90 (0.14)	4.47 (0.16)	5.31 (0.21)	3.45 (0.10)	3.88 (0.11)	4.48 (0.12)	5.35 (0.16)
VT (ml)	534 (13)	478 (5)	474 (5)	461 (5)	445 (5)	480 (4)	475 (4)	461 (4)	443 (4)	479 (2)	474 (2)	459 (2)	439 (2)
VT/kg (ml kg^{-1})	7.63 (0.19)	6.82 (0.07)	6.77 (0.07)	6.59 (0.07)	6.35 (0.07)	6.85 (0.06)	6.79 (0.06)	6.59 (0.06)	6.33 (0.06)	6.85 (0.03)	6.78 (0.03)	6.56 (0.03)	6.28 (0.03)
Minute ventilation (L min^{-1})	16.0 (0.4)	14.3 (0.2)	12.8 (0.1)	11.1 (0.1)	9.3 (0.1)	14.4 (0.1)	12.8 (0.1)	11.1 (0.1)	9.3 (0.1)	14.4 (0.1)	12.8 (0.1)	11.0 (0.0)	9.2 (0.0)
Resp. system compliance (ml cm H_2O^{-1})	22.0 (0.4)	19.4 (0.2)	21.4 (0.2)	24.2 (0.3)	27.8 (0.3)	19.5 (0.2)	21.6 (0.2)	24.5 (0.2)	28.1 (0.2)	19.6 (0.1)	21.8 (0.1)	24.6 (0.1)	28.1 (0.1)
Lung compliance (ml cm H_2O^{-1})	26.0 (0.6)	22.4 (0.3)	25.1 (0.3)	29.1 (0.4)	34.5 (0.5)	22.6 (0.2)	25.5 (0.3)	29.5 (0.3)	34.9 (0.4)	22.7 (0.1)	25.6 (0.1)	29.6 (0.2)	35.0 (0.2)
Dynamic strain	0.32 (0.00)	0.29 (0.00)	0.29 (0.00)	0.28 (0.00)	0.27 (0.00)	0.29 (0.00)	0.29 (0.00)	0.28 (0.00)	0.27 (0.00)	0.29 (0.00)	0.29 (0.00)	0.28 (0.00)	0.27 (0.00)
Static strain	0.20 (0.01)	0.45 (0.01)	0.42 (0.01)	0.39 (0.01)	0.36 (0.01)	0.69 (0.01)	0.67 (0.01)	0.65 (0.01)	0.63 (0.01)	0.91 (0.02)	0.89 (0.02)	0.87 (0.02)	0.85 (0.02)
Total strain	0.53 (0.01)	0.74 (0.01)	0.70 (0.01)	0.67 (0.01)	0.63 (0.01)	0.98 (0.02)	0.96 (0.02)	0.93 (0.02)	0.89 (0.02)	1.20 (0.02)	1.18 (0.02)	1.15 (0.02)	1.12 (0.02)
Total stress (cm H_2O)	51.2 (0.4)	74.8 (1.1)	64.6 (1.0)	53.9 (0.9)	43.7 (0.7)	92.3 (1.0)	80.1 (0.9)	67.5 (0.8)	55.5 (0.6)	107.9 (0.9)	93.9 (0.8)	79.7 (0.7)	66.1 (0.6)
Driving pressure (cm H_2O)	24.3 (0.1)	24.6 (0.0)	22.2 (0.0)	19.1 (0.0)	16.0 (0.0)	24.5 (0.0)	22.0 (0.0)	18.9 (0.0)	15.8 (0.0)	24.4 (0.0)	21.8 (0.0)	18.7 (0.0)	15.6 (0.0)
Power (J min^{-1})	16.2 (0.4)	15.0 (0.1)	11.8 (0.1)	8.6 (0.1)	5.9 (0.0)	15.0 (0.1)	11.8 (0.1)	8.5 (0.1)	5.8 (0.0)	14.9 (0.1)	11.6 (0.0)	8.4 (0.0)	5.7 (0.0)
Pleural pressure swing (cm H_2O)	35.9 (0.2)	36.9 (0.0)	35.8 (0.0)	30.1 (0.1)	24.5 (0.0)	36.3 (0.0)	34.9 (0.0)	29.2 (0.0)	23.6 (0.0)	35.8 (0.0)	34.2 (0.0)	28.4 (0.0)	22.9 (0.0)
Transpulmonary pressure swing (cm H_2O)	20.6 (0.1)	21.3 (0.0)	18.9 (0.0)	15.9 (0.0)	12.9 (0.0)	21.2 (0.0)	18.7 (0.0)	15.7 (0.0)	12.7 (0.0)	21.1 (0.0)	18.5 (0.0)	15.5 (0.0)	12.6 (0.0)

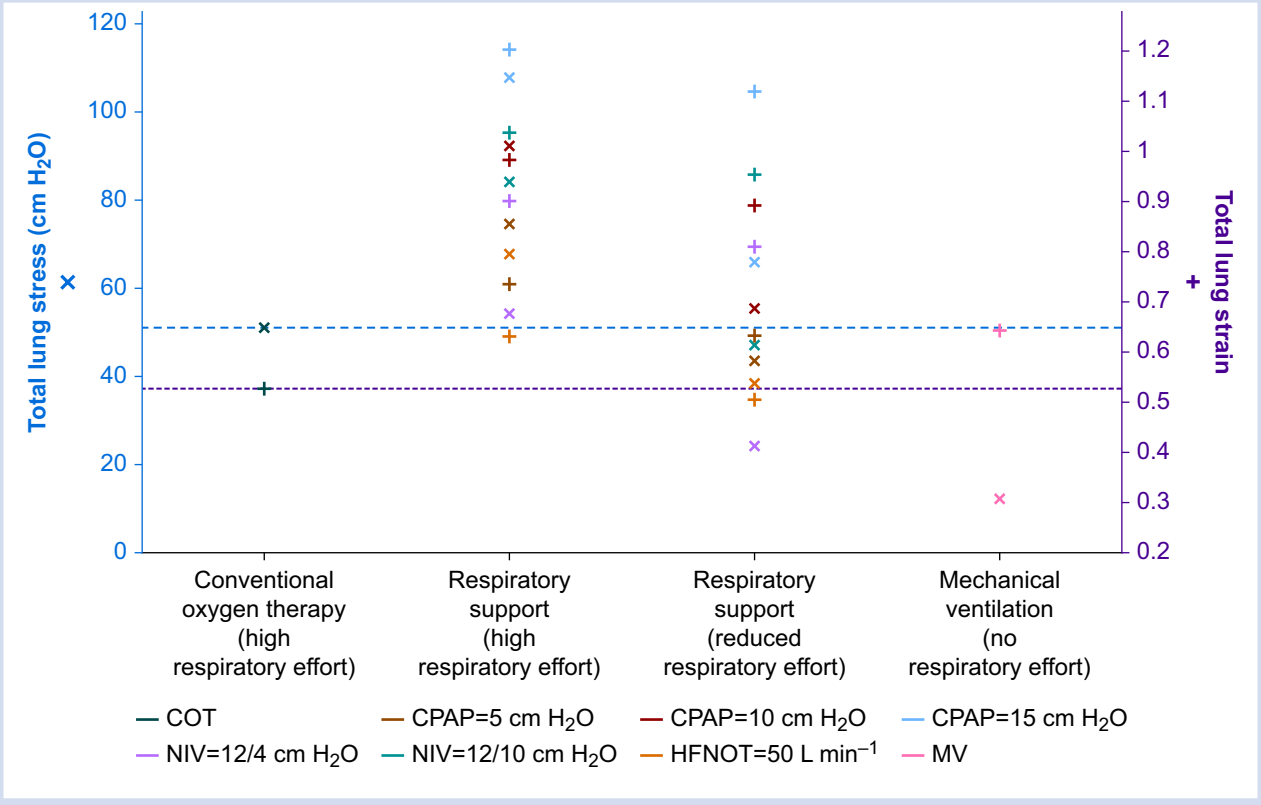

Fig 2. Effects of COT, CPAP, NIV, HFNOT, and protective mechanical ventilation (MV) on total lung stress and strain at high and reduced respiratory effort. Mean values across the cohort of 120 virtual patients. ×, total lung stress; +, total lung strain. COT, conventional oxygen therapy; CPAP, continuous positive airway pressure; HFNOT, high-flow nasal oxygen therapy; NIV, noninvasive ventilation.

Table 1). Failure of CPAP to decrease respiratory effort resulted in increased total lung stress and strain at all levels of CPAP (Table 1). At higher CPAP levels, the same reduction in respiratory effort produced smaller reductions in total lung strain. Provided there was a reduction in respiratory effort, CPAP increased respiratory system compliance while reducing driving pressure and mechanical power (Table 1).

High-flow nasal oxygen therapy

HFNOT delivered at a rate of 50 L min^{-1} (FiO_2=1) provided 3 cm H_2O CPAP and improved oxygenation (Fig 2; Table 2). If HFNOT failed to decrease respiratory effort (column RE1, Table 2), total lung stress and strain increased compared with baseline values. Reduced respiratory effort (equivalent to a reduction in pleural pressure swing of 12 cm H_2O) lowered total lung strain/stress to/below baseline levels but maintained an improvement in oxygenation. When HFNOT reduced respiratory effort, respiratory system compliance was higher compared with baseline values, accompanied by reduced driving pressure and mechanical power (Table 2).

Noninvasive ventilation

NIV delivering FiO_2 of 0.6 (pressure support=12 cm H_2O; PEEP=10 cm H_2O) improved oxygenation (Fig 2; Table 3). Failure to reduce respiratory effort resulted in higher total lung stress and strain. A reduction in respiratory effort (equivalent to a reduction in pleural pressure swing of 14 cm H_2O) lowered total lung stress but total strain remained elevated at around twice baseline values (Table 3). Lowering PEEP to 4 cm H_2O also improved oxygenation and reduced total lung stress, but failed to lower total lung strain even after the maximum reduction in respiratory effort.

Lung-protective, invasive mechanical ventilation

When the patient was sedated (spontaneous respiratory effort set to zero) to facilitate protective mechanical ventilation (tidal volume: 7 ml kg^{-1}; PEEP 5 cm H_2O; RR=20 bpm; I/E ratio 1:3, FiO_2=0.6), oxygen saturation and Pao_2 increased. Total lung stress, driving pressure, power, pleural pressure swing, and transpulmonary pressure swing were all reduced substantially (Table 4). Total lung strain was higher compared with COT and HFNOT, but lower than strain levels observed after CPAP and NIV. Reducing VT to 6 ml kg^{-1} and increasing PEEP to 9 cm H_2O produced similar levels of oxygenation but higher total lung strain.

Effect of higher TOPs for noninvasive and invasive modes of ventilation

Increasing the TOPs of collapsed alveolar compartments in each simulation by 50% produced uniformly poorer

Table 2 Effect of applying HFNOT. HFNOT data are compared with the baseline case of a patient receiving COT and breathing with high respiratory effort (RE1). Respiratory effort decreases progressively from RE1 to RE4. Red squares indicate increases in indices of lung injury >5%, green squares indicate reductions in indices of lung injury >5%, orange squares indicate a change of <5%. COT, conventional oxygen therapy; CPAP, continuous positive airway pressure; HFNO, high-flow nasal oxygen.

	COT	HFNO=50 L min^{-1}, 3 cm H_2O CPAP			
	RE1	RE1	RE2	RE3	RE4
PEEP (cm H_2O)	0.00	2.00	2.00	2.00	2.00
Respiratory rate (bpm)	30.00	30.00	27.00	24.00	21.00
Muscle pressure (cm H_2O)	–26.00	–26.00	–23.00	–20.00	–17.00
SaO_2 (%)	92.1 (1.9)	97.7 (1.4)	95.0 (2.9)	91.8 (4)	91.7 (4.1)
PaO_2 (kPa)	8.28 (0.80)	14.24 (4.02)	10.60 (2.54)	8.81 (2.03)	9.06 (1.92)
Shunt (%)	32.8 (3.1)	31.4 (3.2)	36.1 (4.5)	40.4 (5.4)	40.4 (5.4)
$PaCO_2$ (kPa)	3.33 (0.26)	3.52 (0.19)	3.98 (0.23)	4.53 (0.26)	5.30 (0.34)
VT (ml)	534 (13)	473 (7)	467 (8)	453 (9)	438 (8)
VT/kg (ml kg^{-1})	7.63 (0.19)	6.76 (0.11)	6.67 (0.11)	6.47 (0.12)	6.26 (0.12)
Minute ventilation (L min^{-1})	16.0 (0.4)	14.2 (0.2)	12.6 (0.2)	10.9 (0.2)	9.2 (0.2)
Resp. system compliance (ml cm H_2O^{-1})	22.0 (0.4)	19.2 (0.3)	21.0 (0.4)	23.7 (0.4)	27.3 (0.5)
Lung compliance (ml cm H_2O^{-1})	26.0 (0.6)	22.1 (0.4)	24.6 (0.5)	28.3 (0.6)	33.6 (0.8)
Dynamic strain	0.32 (0.00)	0.29 (0.00)	0.28 (0.00)	0.27 (0.00)	0.26 (0.00)
Static strain	0.20 (0.01)	0.35 (0.01)	0.30 (0.01)	0.27 (0.01)	0.24 (0.01)
Total strain	0.53 (0.01)	0.63 (0.01)	0.59 (0.01)	0.54 (0.01)	0.51 (0.01)
Total stress (cm H_2O)	51.2 (0.4)	67.9 (1.0)	58.0 (1.1)	47.8 (0.9)	38.5 (0.8)
Driving pressure (cm H_2O)	24.3 (0.1)	24.7 (0.0)	22.2 (0.0)	19.1 (0.0)	16.1 (0.0)
Power (J min^{-1})	16.2 (0.4)	14.9 (0.2)	11.7 (0.2)	8.5 (0.1)	5.9 (0.1)
Pleural pressure swing (cm H_2O)	35.9 (0.2)	37.1 (0.1)	36.3 (0.1)	30.5 (0.0)	24.9 (0.0)
Transpulmonary pressure swing (cm H_2O)	20.6 (0.1)	21.4 (0.1)	19.0 (0.1)	16.0 (0.1)	13.0 (0.1)

Table 3 Effect of applying NIV with different levels of PEEP. Comparison of the effect of applying NIV with different levels of PEEP *vs* the baseline case of a patient receiving COT and breathing with high respiratory effort (RE1). Respiratory effort decreases progressively from RE1 to RE4. Red squares indicate increases in indices of lung injury >5%, green squares indicate reductions in indices of lung injury >5%, orange squares indicate a change of <5%. COT, conventional oxygen therapy; NIV, noninvasive ventilation; PSV, pressure support ventilation.

	COT	NIV: PSV=12 cm H_2O, PEEP=4 cm H_2O				NIV: PSV=12 cm H_2O, PEEP=10 cm H_2O			
	RE1	RE1	RE2	RE3	RE4	RE1	RE2	RE	RE4
PEEP (cm H_2O)	0.00	4.00	4.00	4.00	4.00	10.00	10.00	10.00	10.00
Respiratory rate (bpm)	30.00	30.00	27.00	24.00	21.00	30.00	27.00	24.00	21.00
Muscle pressure (cm H_2O)	–26.00	–26.00	–23.00	–20.00	–17.00	–26.00	–23.00	–20.00	–17.00
SaO_2 (%)	92.1 (1.9)	96.9 (1.0)	95.4 (1.6)	93.7 (1.6)	93.4 (1.9)	96.9 (1.0)	96.8 (1.0)	96.8 (1.0)	96.7 (1.0)
PaO_2 (kPa)	8.28 (0.80)	11.52 (1.32)	10.16 (1.44)	8.93 (0.84)	8.86 (0.94)	11.59 (1.0)	11.57 (1.36)	11.54 (1.33)	11.48 (1.29)
Shunt (%)	32.8 (3.1)	24.1 (2.3)	27.2 (3.3)	30.6 (2.8)	31.0 (3.4)	24.0 (2.4)	24.0 (2.4)	24.1 (2.4)	24.2 (2.3)
$PaCO_2$ (kPa)	3.33 (0.26)	2.41 (0.12)	2.59 (0.13)	2.83 (0.14)	3.11 (0.15)	3.09 (0.10)	3.42 (0.11)	3.86 (0.11)	4.44 (0.13)
VT (ml)	534 (13)	686 (7)	705 (8)	716 (8)	732 (9)	533 (3)	531 (3)	523 (3)	513 (3)
VT/kg (ml kg^{-1})	7.63 (0.19)	9.80 (0.10)	10.07 (0.11)	10.22 (0.12)	10.46 (0.12)	7.61 (0.04)	7.59 (0.04)	7.47 (0.04)	7.32 (0.04)
Minute ventilation (L min^{-1})	16.0 (0.4)	20.6 (0.2)	19.0 (0.2)	17.2 (0.2)	15.4 (0.2)	16.0 (0.1)	14.3 (0.1)	12.5 (0.1)	10.8 (0.1)
Resp. system compliance (ml cm H_2O^{-1})	22.0 (0.4)	28.7 (0.3)	33.2 (0.4)	39.7 (0.4)	49.0 (0.6)	21.9 (0.1)	24.5 (0.1)	28.2 (0.2)	33.2 (0.2)
Lung compliance (ml cm H_2O^{-1})	26.0 (0.6)	35.9 (0.5)	43.1 (0.6)	54.7 (0.8)	74.2 (1.3)	25.8 (0.2)	29.5 (0.1)	35.0 (0.3)	43.1 (0.3)
Dynamic strain	0.32 (0.00)	0.41 (0.00)	0.43 (0.00)	0.43 (0.00)	0.44 (0.00)	0.32 (0.00)	0.32 (0.01)	0.32 (0.00)	0.31 (0.00)
Static strain	0.20 (0.01)	0.49 (0.01)	0.44 (0.01)	0.40 (0.01)	0.37 (0.01)	0.72 (0.02)	0.69 (0.01)	0.67 (0.01)	0.64 (0.01)
Total strain	0.53 (0.01)	0.90 (0.02)	0.87 (0.01)	0.83 (0.01)	0.81 (0.01)	1.04 (0.02)	1.01 (0.02)	0.98 (0.02)	0.95 (0.02)
Total stress (cm H_2O)	51.2 (0.4)	54.4 (0.4)	44.0 (0.5)	33.6 (0.4)	24.2 (0.3)	84.2 (0.8)	72.3 (0.7)	59.5 (0.6)	47.2 (0.5)
Driving pressure (cm H_2O)	24.3 (0.1)	23.9 (0.0)	21.2 (0.0)	18.0 (0.0)	14.9 (0.0)	24.3 (0.0)	21.7 (0.0)	18.6 (0.0)	15.5 (0.0)
Power (J min^{-1})	16.2 (0.4)	19.3 (0.1)	15.3 (0.1)	11.0 (0.1)	7.4 (0.0)	16.2 (0.1)	12.7 (0.1)	9.2 (0.0)	6.3 (0.0)
Pleural pressure swing (cm H_2O^{-1})	35.9 (0.2)	33.5 (0.1)	30.4 (0.1)	24.1 (0.1)	17.8 (0.1)	35.5 (0.0)	33.6 (0.1)	27.7 (0.1)	21.9 (0.1)
Transpulmonary pressure swing (cm H_2O)	20.6 (0.1)	19.1 (0.1)	16.4 (0.1)	13.1 (0.0)	9.9 (0.1)	20.6 (0.0)	18.0 (0.0)	14.9 (0.0)	11.9 (0.0)

outcomes for CPAP and NIV (Supplementary Figure S7.1), with marginal improvements in oxygenation and increased total lung strain (Supplementary Table S7.2). Higher PEEP reduced compliance because of alveolar over-distension and a lack of recruitment.[13] In contrast, the benefits of improving oxygenation with HFNOT persisted, accompanied by large reductions in respiratory effort and reducing total lung stress and strain to values at or below baseline (Supplementary Table S7.3). Lung-protective mechanical ventilation improved oxygenation while reducing all indices of lung injury except for total lung strain (Supplementary Table S7.4).

Table 4 Effect of applying protective mechanical ventilation under full sedation. A comparison of the effect of applying protective mechanical ventilation under full sedation with a patient receiving conventional oxygen therapy (COT) and breathing with high respiratory effort (RE1). Red squares indicate increases in indices of lung injury >5%, green squares indicate reductions in indices of lung injury >5%, orange squares indicate a change of <5%.

	COT	VT=7 ml kg^{-1}, PEEP=5 cm H_2O, FiO_2=0.6	VT=6 ml kg^{-1}, PEEP=9 cm H_2O, FiO_2=0.6
PEEP (cm H_2O)	0.00	5.00	9.00
Respiratory rate (bpm)	30.00	20	20
Muscle pressure (cm H_2O)	–26.00	0	0
SaO_2 (%)	92.1 (1.9)	92.5 (1.7)	91.8 (1.7)
PaO_2 (kPa)	8.28 (0.80)	8.68 (0.72)	8.92 (0.69)
Shunt (%)	32.8 (3.1)	32.2 (2.9)	32.8 (2.8)
$PaCO_2$ (kPa)	3.33 (0.26)	5.01 (0.16)	6.09 (0.15)
VT (ml)	534 (13)	481 (0)	412 (0)
VT/kg (ml kg^{-1})	7.63 (0.19)	6.87 (0.00)	5.88 (0.00)
Minute ventilation (L min^{-1})	16.0 (0.4)	9.6 (0.0)	8.2 (0.0)
Resp. system compliance (ml cm H_2O^{-1})	22.0 (0.4)	66.8 (0.7)	62.5 (0.6)
Lung compliance (ml cm H_2O^{-1})	26.0 (0.6)	124.7 (2.3)	110.5 (1.8)
Dynamic strain	0.32 (0.00)	0.29 (0.01)	0.25 (0.00)
Static strain	0.20 (0.01)	0.35 (0.01)	0.54 (0.01)
Total strain	0.53 (0.01)	0.64 (0.01)	0.79 (0.01)
Total stress (cm H_2O)	51.2 (0.4)	12.2 (0.2)	16.0 (0.3)
Driving pressure (cm H_2O)	24.3 (0.1)	7.2 (0.1)	6.6 (0.1)
Power (J min^{-1})	16.2 (0.4)	1.8 (0.0)	1.5 (0.0)
Pleural pressure swing (cm H_2O)	35.9 (0.2)	1.9 (0.0)	1.8 (0.0)
Transpulmonary pressure swing (cm H_2O)	20.6 (0.1)	3.9 (0.1)	3.7 (0.1)

Discussion

In this study we used a computational simulator of COVID-19 pathophysiology to quantify the effects of COT, HFNOT, CPAP, and NIV in 120 virtual patients. To our knowledge, this is the first study in COVID-19 to provide data with which the effects of these three different types of noninvasive respiratory support on lung mechanics can be directly compared. The conceptual model for using respiratory support in COVID-19 illustrated in Fig 1 is supported by our results — application of HFNOT, CPAP, and NIV improves oxygenation but also increases stress and strain on the lung if high respiratory effort is maintained. Reduced respiratory effort is required in order to minimise lung injury and ensure that the oxygenation benefit of the provided respiratory support is also 'protective'. Indeed, in the presence of high respiratory effort, indices of lung injury under all forms of noninvasive respiratory support considered were uniformly higher than those produced by protective mechanical ventilation.

Our results may be particularly relevant to patients with early-stage COVID-19 pneumonia, who are often poorly recruitable — that is their hypoxaemia is typically not the result of widespread alveolar collapse.[5] Interestingly, however, our data align well with (and provide a potential explanation for) the results of a study into NIV conducted on 30 patients with acute hypoxic respiratory failure shortly before the COVID-19 pandemic,[14] which showed that a significant reduction of respiratory effort (equivalent to a decrease in pleural pressure swing, measured by oesophageal manometry, of 10 cm H_2O or more after 2 h of NIV) was strongly associated with avoidance of intubation and represented the most accurate predictor of treatment success. Reductions in pleural pressure swings of 10 cm H_2O or more after initiation of respiratory support were typically required in our simulations to bring total lung stress and strain back down to acceptable levels.

In our simulations, the effectiveness of both CPAP and NIV was highly sensitive to the values of TOPs in the collapsed lung regions. Increasing the average value for the TOPs by 50% severely curtailed the effectiveness of both therapies in improving oxygenation — even when this was achieved (using a CPAP of 15 cm H_2O), the resulting levels of lung stress and strain (even after a reduction in respiratory effort) are likely to be compatible with the development of P-SILI.[9] Previous data suggest that a wide range of alveolar opening pressures exist in ARDS — one study of five patients (with an average of 6% of the lung parenchyma available for recruitment) found the maximal frequency of estimated TOPs to be approximately 20 cm H_2O in three patients, whereas in two other patients this maximal frequency occurred between 35 and 40 cm H_2O.[10] This wide distribution of estimated TOPs may reflect the particular nature of the underlying atelectasis, as pressures needed to reverse collapse of the small airways are generally lower than those required to reopen reabsorption atelectasis.[10] It is thus tempting to speculate that, because early-stage COVID-19 patients typically have low levels of gasless tissue, but highly variable recruitability, differences in TOP owing to different types of COVID-19-induced collapse could be important in determining recruitability and hence response to CPAP and NIV.

A recent large clinical RCT found that CPAP significantly reduced the risk of tracheal intubation compared with COT, among patients with acute hypoxaemic respiratory failure because of COVID-19.[2] Our data comparing the levels of stress and strain applied to the lung by HFNOT, CPAP, and NIV, suggest that HFNOT may be a more protective form of respiratory support for many patients with COVID-19, and

particularly for patients with poorer recruitability (see Supplementary Tables S1–S3). Further clinical RCTs trials are recommended in order to confirm these results.

Our study has several limitations. The results are based on computational modelling of mechanisms that have been proposed to underlie COVID-19 pathophysiology, rather than on models matched to detailed individual data from patients with COVID-19. Accordingly, some model parameters were manually adjusted to give outputs that match reported data on COVID-19 patients, rather than being fit to data that explicitly define the parameters. The model also neglects some physiological realities (namely spatial interdependence of alveoli, non-uniformity of diaphragmatic contraction, and gravitational effects) which would act to produce higher values of certain lung injury indices in particular lung regions. These limitations must be balanced against the unique strength of our computational modelling approach – that it allows precise quantitative comparison of different noninvasive (and protective invasive) ventilatory strategies on an identical virtual patient population.

In summary, our results suggest that, although noninvasive respiratory support uniformly improves oxygenation, reductions in respiratory effort are also required to confer a net positive effect on the total stress and strain applied to the lung. In the absence of such reductions, or when pressures applied are high, damage to the lung via self-inflicted lung injury is possible. In our virtual patient cohort, HFNOT produced similar oxygenation improvements while applying lower stresses/strains to the lung than CPAP or NIV, particularly in patients with poorer recruitability. In the presence of high respiratory effort, indices of lung injury under noninvasive respiratory support were generally higher than those produced by invasive ventilation using protective settings and control of driving pressure.

Authors' contributions

Principal modeller: LW.
Modelling and technical review: AD, SS, DGB, JGH.
Original concept, study design: DGB, JGH, LC, TES, MC.
All authors contributed to the drafting of the manuscript.

Declarations of interest

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Appendix A. Supplementary data

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