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Why reduced inspiratory pressure could determine success of non-invasive ventilation in acute hypoxic respiratory failure

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Abstract— **The magnitude of inspiratory effort relief within the first 2 hours of non-invasive ventilation for hypoxic respiratory failure was shown in a recent exploratory clinical study to be an early and accurate predictor of outcome at 24 hours. We simulated the application of non-invasive ventilation to three patients whose physiological and clinical characteristics match the data in that study. Reductions in inspiratory effort corresponding to reductions of esophageal pressure swing greater than 10 cmH_2O more than halved the values of total lung stress, driving pressure, power and transpulmonary pressure swing. In the absence of significant reductions in inspiratory pressure, multiple indicators of lung injury increased after application of non-invasive ventilation.**

Clinical Relevance— **We show using computer simulation that reduced inspiratory pressure after application of noninvasive ventilation translates directly into large reductions in multiple well-established indicators of lung injury, providing a potential physiological explanation for recent clinical findings.**

I. Introduction

The role of non-invasive ventilation (NIV) in patients with acute hypoxic respiratory failure (AHRF) is the subject of much debate within the medical community. NIV is widely used to maintain spontaneous breathing in patients with AHRF, which can help to preserve respiratory muscle function, improve gas-exchange and regional ventilation [1], and reduce sedation and days of invasive mechanical ventilation (MV) [2]. However, recent studies have also suggested that spontaneous breathing might also have the potential to cause so-called patient self-inflicted lung injury (P-SILI) [3,4].

A recent exploratory clinical trial [5] found that a reduction in inspiratory effort after the application of NIV was strongly associated with avoidance of intubation and represented the most accurate predictor of treatment success. The study included 30 patients with moderate to severe AHRF (median baseline PF ratio of 125 mmHg), and suggested a reduction of pleural pressure swing, as measured by esophageal manometry, of more than 10 cmH_2O within 2 hours of initiation of NIV as a threshold for predicting treatment success. Despite the compelling evidence produced by this study, there is a lack of clarity as to exactly why reduction of inspiratory effort should play such a crucial role determining the course of NIV treatment. The study authors hypothesized that high inspiratory effort over time might be a potential mechanism of lung damage enhancement if acute respiratory distress is severe. However, clinicians face multiple challenges in obtaining high quality data from spontaneously breathing patients with which to confirm this hypothesis – NIV equipment provides few patient measurements, and bedside measurements rely on patient cooperation in activities such as respiratory holds and swallowing esophageal balloons, uncomfortable tasks exacerbated by the sensation of dyspnea many of these patients are experiencing.

Computational modelling offers an attractive alternative for investigating these issues, since it allows for accurate calculation of multiple physiological variables which could potentially lead to patient self-inflicted lung injury (P-SILI). Many of these values are extremely difficult to measure at the bedside, but computational modelling allows for them to be easily computed based on different patient physiological characteristics and at multiple levels of inspiratory effort.

To investigate the physiological factors which could determine NIV success and failure, we created three virtual patients with characteristics that are representative of the patient cohort described in [5] before application of NIV, i.e. while being treated with high flow nasal oxygen (HFNO) of 60 L/min at an FiO_2 of 100%. NIV was then applied to each of the virtual patients, following the protocol for adjusting inspiratory and expiratory pressures described in [5]. Inspiratory effort on the part of the patient was then changed to match the mean changes seen in both success and failure cases after two hours of NIV treatment. Our results indicate that reductions in inspiratory effort corresponding to those found in [5] more than halved the values of several indicators of lung injury, whereas these values increased after application of NIV in the absence of reduced inspiratory effort.

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II. METHODS

A. The Cardiopulmonary Simulator

The simulator used to conduct this study is a multi-compartmental cardiopulmonary model which has previously been used in studies of both mechanically ventilated and spontaneously breathing patients. The simulator represents multiple interacting organ systems and incorporates a high level of physiological detail, including multiple alveolar compartments, multi-compartmental gas exchange, viscoelastic compliance behavior, interdependent blood-gas solubility and hemoglobin behavior and heterogeneous distributions of pulmonary ventilation and perfusion. The simulator includes 100 heterogeneous alveolar compartments with independently configurable mechanical properties which can be used to represent varying levels of alveolar collapse, ventilation-perfusion mismatch, physiological shunt and deadspace, alveolar gas trapping, and disruption of gas exchange.

Each model component is described as several mass conserving functions and solved as algebraic equations, obtained, or approximated from the published literature, experimental data, and clinical observations. These equations are solved in series in an iterative manner so that solving one equation at the current time instant determines the values of the independent variables in the next equation. At the end of each iteration, the results of the solution of the final equations determine the independent variables of the first equation for the next iteration. The iterative process continues for a predetermined time, with each iteration representing a 'time slice' t of real physiological time (set to 30 ms).

The spontaneous breathing module within the simulator was first implemented during a study into the risk of P-SILI in patients with early COVID-19 pneumonia [4], based on the work in [6] and [7]. The module represents the pressure generated by the respiratory muscles with a piecewise function consisting of a parabolic profile during the inspiratory phase and an exponential function during the expiratory phase. Further details and the governing equations relating to this module can be found in [4].

A diagrammatic interpretation of the simulator can be found in Figure 1, whilst a more detailed description of the underlying mathematics can be found in the supplementary material which accompanies [4].

B. Virtual Patient Characteristics

For this study, three virtual patients were generated to represent the patient cohort described in the trial manuscript. The virtual patients were fit to the trial data by manually adjusting levels of poorly and non-aerated alveoli in the model to match the range of PF ratios in [5] with the same baseline respiratory effort and oxygen support. Levels of non-aerated and poorly aerated alveoli were set within the simulator by altering the number of alveolar compartments that are collapsed and have disruption to gas exchange, respectively. Care was also taken to ensure that each virtual patient's baseline $PaCO_2$ was below 45 mmHg so that they were not initially suffering from hypercapnic respiratory failure, an exclusion criterion for the trial.

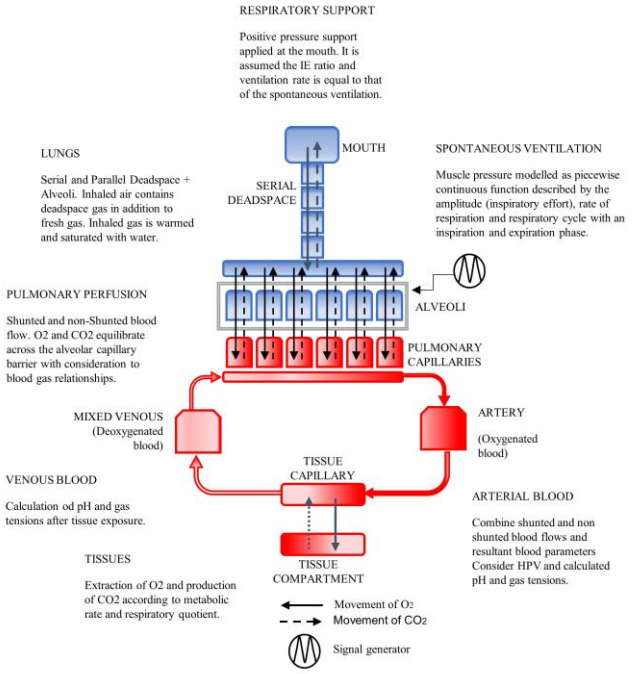

Figure 1. Diagrammatic representation of the simulator

Compartments with disrupted gas exchange were used to represented poorly ventilated regions of the lung as a result of being partially fluid filled. In these compartments gas exchange was reduced to 10% of that which can take place in the healthy compartments. Collapsed alveolar compartments had their threshold opening pressures (TOP) and threshold closing pressures (TCP) adjusted appropriately. To generate the values for each compartment, normal distributions were generated for TOP and TCP with means of 28.97 ± 10.09 cmH_2O and 5.02 ± 2.02 cmH_2O, based on the data in [8].

These distributions were then sampled to give the values required for each of the collapsed compartments. A comparison of the physiological characteristics of the cohort described in [5], and the virtual patients created for this study, can be found in Table 1.

C. Modelling Non-Invasive Ventilation

Patients were initially simulated breathing spontaneously at the baseline conditions specified in [5], i.e HFNO of 60 L/min at 100% FiO_2. To simulate this, patients were run on the spontaneous breathing module of the simulator as described in a previous study [4] in addition to a constant pressure of 4 cmH_2O throughout the respiratory cycle to reflect the pressures generated by HFNO of 60 L/min [9].

TABLE I. PATIENT BASELINE CHARACTERISTICS

Patient ID	Patient data from [5]	1	2	3
Respiratory Rate (bpm)	36 (27- 44)	36	36	36
Pleural (Esophageal) Pressure Swing (cmH_2O)	35 (26 - 40)	35.1	35.0	35.0
BMI ($kg\ m^{-2}$)	23 (19 - 27)	23.1	23.1	23.1
PF Ratio (mmHg)	125 (101 -170)	101.6	123.7	148.6
$PaCO_2$ (mmHg)	35 (30 - 40)	37.8	36.1	35.0

In accordance with the clinical trial protocol, the patients were then switched to NIV with initial values for PEEP and pressure support set to 6 cmH_2O and 10 cmH_2O respectively. The value for PEEP was then adjusted within the range 4 – 8 cmH_2O to give an $SaO_2 > 92\%$ for an $FiO_2 < 70\%$.

The inspiratory effort was then changed according to the levels seen in the two groups of patients in [5] who avoided intubation or death (NIV success) or who were subsequently intubated or died (NIV failure). For the NIV success case, this corresponded to reducing respiratory rate in the simulated patients from 36 bpm to 30 bpm (clinical trial data: reduction from 36 (27–45) to 30 (24-37) bpm) and reducing pleural pressure swings (equivalent to esophageal pressure swing, ΔPes) from 35 to 11.0 cmH_2O (clinical trial data: reduction from 32.5 (24-39) to 11 (8-15) cmH_2O). For the NIV failure case, this corresponded to reducing respiratory rate in the simulated patients from 36 bpm to 31 bpm (clinical trial data: reduction from 34 (27–42) to 31 (25-37) bpm) and reducing pleural pressure swings (equivalent to esophageal pressure swing, ΔPes) from 35 to 31.3 cmH_2O (clinical trial data: reduction of ΔPes from 38 (32-42) to 31.5 (30-36) cmH_2O) respectively.

Measurements of oxygenation, stress, strain, and other lung injury indicators were calculated for each virtual at each level of inspiratory effort as described in [4].

III. Results

Baseline: Under HFNO of 60 L/min with liberal oxygenation ($FiO_2 = 1$), SaO_2 was equal to 97.9%, 98.9%, and 99.4% for patients 1, 2, and 3, respectively, when breathing with high inspiratory effort (RR of 36 bpm, ΔPes of 35 cmH_2O). Shunt ranged from 30.5% to 26.6% across the three patients whilst respiratory system compliance ranged from 13.2 ml/cmH_2O to 13.5 ml/cmH_2O. Patient 1 had a baseline total lung strain of 0.50 whilst patients 2 and 3 both had total lung strain of 0.46. Total lung stress values for the three patients were 48.1 cmH_2O, 50.0 cmH_2O, and 51.0 cmH_2O and ventilatory power ranged from 10.2 J/min to 10.4 J/min.

NIV success: For the success case, NIV was applied with a PEEP of 4 cmH_2O and pressure support of 10 cmH_2O, and a reduction in inspiratory effort corresponding to a ΔPes reduction of 24 cmH_2O was simulated. This produced SaO_2 values of 93.1%, 94.4%, and 95.3% for patients' 1, 2, and 3 respectively, while shunt reduced slightly from the baseline case, ranging from 30.2% to 26.1%. Respiratory system compliance saw a large increase with values ranging from 28.4 ml/cmH_2O to 29.0 ml/cmH_2O. Total lung strain saw a slight reduction with values down of 0.47 for patient 1 and 0.44 for patients 2 and 3. Total lung stress reduced by more than 50% when compared to the baseline case, with values of 18.9 cmH_2O, 19.7 cmH_2O, and 20.1 cmH_2O for patients 1, 2, and 3 respectively. Ventilation power reduced to a third of its initial value, with a value of 3.3 J/min for all three patients. Driving pressure and transpulmonary pressure swing were both reduced by more than 50% to 9.6 cmH_2O and 7.9 cmH_2O, respectively.

TABLE II. Simulation results from 3 virtual patients replicating baseline, NIV success and NIV failure cases reported in [5]

	Baseline			NIV Success (After 2 hours)			NIV Failure (After 2 hours)		
Patient ID	1	2	3	1	2	3	1	2	3
Respiratory Rate (bpm)	36	36	36	30	30	30	31	31	31
Muscle Pressure (cmH_2O)	-23	-23	-23	-11.1	-11.1	-11.1	-25.1	-25.1	-25.1
SaO_2 (%)	97.9	98.9	99.4	93.1	94.4	95.3	97.1	97.8	98.3
PaO_2 (mmHg)	101.6	123.7	148.6	71.2	76.8	81.4	86.9	95.2	104.8
Shunt (%)	30.5	28.2	26.6	30.2	27.8	26.1	23.3	21.6	20.1
$PaCO_2$ (mmHg)	37.8	36.1	35.0	50.0	48.1	46.6	23.3	22.3	21.6
VT (ml)	289	292	295	279	282	285	494	498	504
VT/kg (ml/kg)	4.13	4.17	4.22	3.99	4.03	4.08	7.06	7.12	7.20
Minute Ventilation (L/min)	10.41	10.52	10.64	8.38	8.47	8.56	15.32	15.45	15.61
Resp. System Compliance (ml/cmH_2O)	13.2	13.3	13.5	28.4	28.7	29.0	21.8	21.8	22.1
Lung Compliance (ml/cmH_2O)	14.5	14.7	14.9	35.3	35.8	36.3	25.6	25.7	26.1
Dynamic Strain	0.23	0.22	0.22	0.22	0.21	0.21	0.39	0.38	0.38
Static Strain	0.27	0.24	0.24	0.25	0.23	0.23	0.45	0.39	0.39
Total strain	0.50	0.46	0.46	0.47	0.44	0.44	0.84	0.77	0.76
Total Stress (cmH_2O)	48.1	50.0	51.0	18.9	19.7	20.1	44.3	44.1	44.5
Driving Pressure (cmH_2O)	21.9	21.9	21.9	9.6	9.8	9.8	22.7	22.8	22.8
Power (J/min)	10.2	10.3	10.4	3.3	3.3	3.3	14.5	14.7	14.8
Pleural Pressure Swing (cmH_2O)	35.1	35.0	35.0	11.0	11.0	11.0	31.4	31.3	31.3
Transpulmonary Pressure Swing (cmH_2O)	19.9	19.9	19.9	7.9	7.9	7.9	19.3	19.4	19.3

NIV failure: For the failure case, NIV was again applied with a PEEP of 4 cmH_2O and pressure support of 10 cmH_2O, and a reduction in inspiratory effort corresponding to a ΔPes reduction of 4 cmH_2O was simulated. This produced SaO_2 values of 97.1%, 97.8%, and 98.3% for patients 1, 2, and three respectively. Shunt was significantly reduced from the baseline case, with shunt % now ranging from 23.3% to 20.1% across the cohort. Respiratory system compliance saw a modest increase from baseline, with values ranging from 21.8 ml/cmH_2O to 22.1 ml/cmH_2O. Total lung stress decreased slightly from the baseline values but total lung strain almost doubled, with strains of 0.84, 0.77, and 0.76 for patients 1, 2, and 3 respectively. Ventilation power and driving pressure were both increased from baseline, with values of 14.5 J/min to 14.8 J/min, and 22.7 cmH_2O to 22.8 cmH_2O, respectively.

IV. Discussion and Conclusions

Although widely used in clinical practice regardless of disease severity, the application of NIV to treat patients with AHRF remains a topic of controversy. Despite promising initial results [10,11], more recent studies focusing on patients with AHRF and excluding underlying chronic respiratory diseases or cardiogenic pulmonary edema have suggested that delays in intubation resulting from the use of NIV can increase mortality rates [12,13,14]. However, despite high failure rates in patients with more severe AHRF, successful application of NIV has been independently associated with increased survival and reduced length of ICU stay [12].

To date, the search for the key factors that could determine (and be used to predict) success or failure of NIV treatment has yielded no definitive answers. Previous studies have suggested a number of factors (i.e., higher disease severity score on admission, older age, ARDS or pneumonia as the etiology for acute respiratory failure, or a lack of improvement in blood gas exchange within 1 h of treatment) that could be associated with NIV failure, but in the recent study described in [5] none of these factors differed between the success and failure groups.

The hypothesis suggested in [5] that sufficient reduction of inspiratory pressure soon after initiation of NIV could be the key determinant of its success or failure has a plausible physiological basis, grounded in the arguments for the existence of patient self-inflicted lung injury. If, as has now been suggested by a number of studies [15,16,4], high respiratory efforts can damage injured lungs even in the case of purely spontaneous breathing, it seems reasonable that such efforts when combined with additional pressures generated by NIV could potentially, over time, lead to the accumulation of injury and eventual deterioration in the patient's condition. The results presented here directly support this hypothesis, since they show that, in the absence of significantly reduced inspiratory effort, application of NIV can produce increases in multiple well-established indicators of lung injury.

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