Proning reduces ventilation heterogeneity in patients with elevated BMI: implications for COVID-19 pneumonia management?

To the Editor:

Coronavirus disease 2019 (COVID-19) is caused by a novel zoonotic coronavirus known as severe acute respiratory syndrome coronavirus 2 and has been identified as a pandemic by the World Health Organization (WHO) [1]. Several risk factors have been identified for severe COVID-19-associated pneumonia, with obesity identified as a significant and independent risk factor for death [2].

A number of potential mechanisms may account for the increased risk of mortality in obese patients with COVID-19. These include: the known association between obesity and thromboembolic disease [3]; immune dysregulation promoted by adipose tissue in obese patients [4]; associated comorbidities hypertension and diabetes, which are risk factors for COVID-related mortality [2]; and the mechanical effects of obesity itself on the lung, which promote alveolar hypoventilation, atelectasis and hypoxia, particularly when patients are supine [5, 6]. Recent reports in early COVID-19 pneumonia have suggested that when awake, self-proning improved oxygen saturations in patients presenting to emergency departments with COVID-19 pneumonia [7].

Here, we sought to use previously reported patient-based computational airway models derived from computed tomography (CT) [8, 9] to: 1) evaluate the impact of simulated proning in obese and non-obese patients on lung ventilation and its heterogeneity; and 2) translate the observations in lung models to identify how best to stratify patients for self-proning using body mass index (BMI).

To investigate the effect of proning on patients with varying BMI, we retrieved inspiratory CT-derived, patient-based lung structures for 31 subjects (11 healthy, 20 asthmatic), with full details reported in a prior study [8, 9]. Briefly, each structure consisted of a combination of CT-extracted airways (to an average generation 7), from which a further 9 generations of airways were algorithmically grown, within identified lobar boundaries (airways in each structure: 55319 [45077, 61543]). Across a large variety of studies, these airway structures have been shown to meaningfully capture diffuse small airways lung disease, and to allow for accurate simulations of ventilation, and pulmonary gas transport [10, 11].

Using a prior published model of ventilation in varying body positions [9], we simulated ventilation (a 1-L inhalation, starting from functional residual capacity) in the 31 patient-based structures, in both supine and prone positions. In line with previous studies, body position changes were simulated by enforcing a gravitational gradient on pleural pressure in the sagittal axis (using a gravitational strength of $1.5\%\cdot cm^{-1}$ [9]). To quantify ventilation heterogeneity (VH), we measured the variance in alveolar volumes (the volumes subtending each terminal conducting bronchiole), and calculated ventilation ratios (the ratio of inspired volume to a region, over total volume at peak inspiration).

The 31 subjects were made up of: 20 subjects with asthma and 11 healthy volunteers; 12 males and 19 females; with a median (interquartile range) age 59 (46–65) yrs, BMI 25 (24–30) $kg\cdot m^{-2}$ and forced

expiratory volume in 1 s/forced vital capacity 0.77 (0.73–0.81). Across all subjects, there was a positive correlation between the degree of improvement in VH when moving from supine to prone (Pearson's correlation coefficient 0.64; p=0.0001) and the subject BMI (figure 1a). Obese patient structures (BMI >30 kg·m^{-2}) exhibited a significantly greater decrease in alveolar volume variance (p=0.001, unpaired t-test) than non-obese patients (figure 1b). A weaker but still significant difference was also seen when comparing overweight (BMI >25 kg·m^{-2}) patient structures to those with a BMI ⩽25 kg·m^{-2} (p-value=0.019). These differences in ventilation improvement are reflected in the alveolar volume distributions of high- and low-BMI patients (figure 1c), with the high-BMI patient's volume distribution narrowing significantly when proned, behaviour that is not seen in the low-BMI patient. In fact, non-overweight patient structures exhibited a small but statistically significant (p<0.0001, one-sided t-test) worsening of ventilation when proned (figure 1a). No significant gender-based effect was seen, with
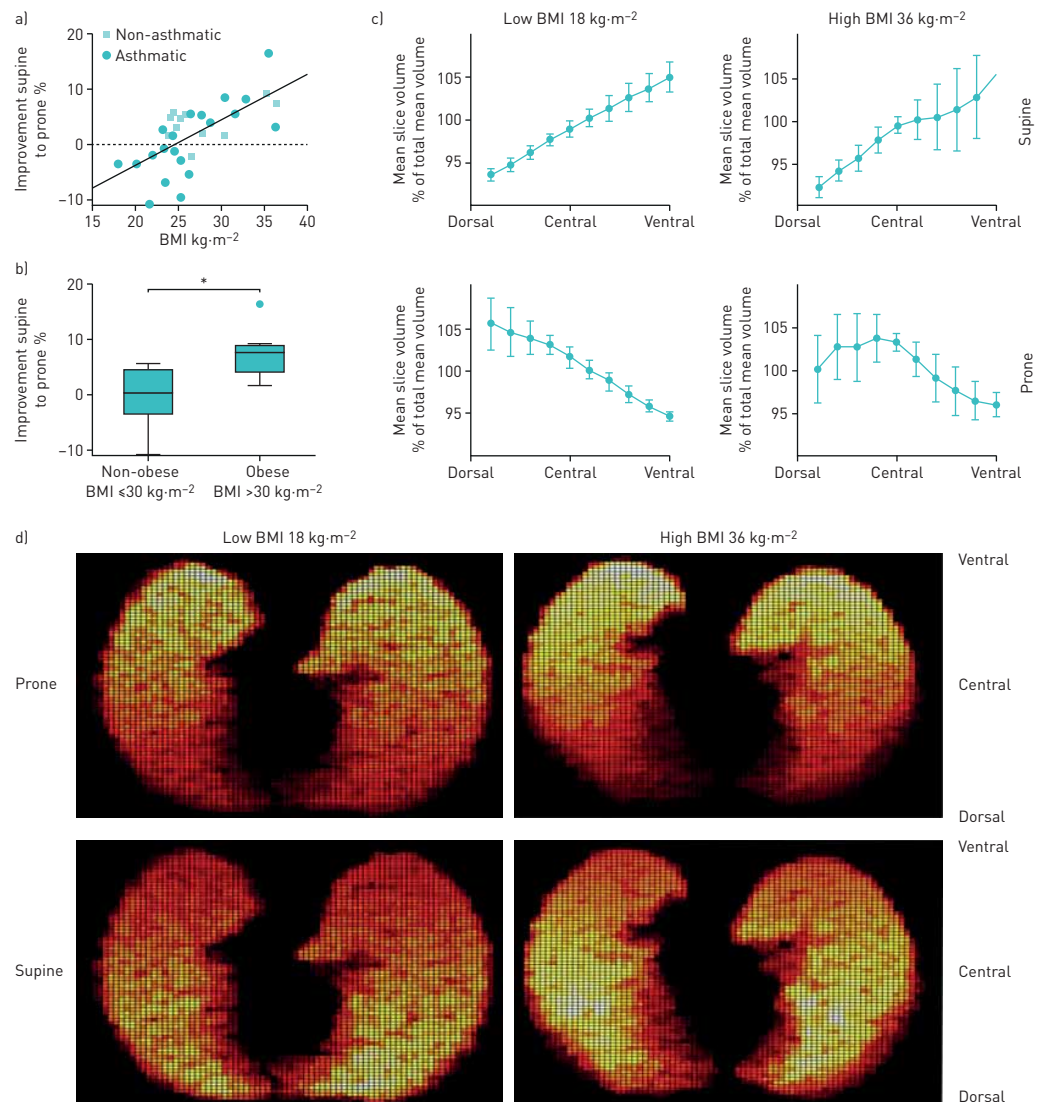
FIGURE 1 Comparative ventilation heterogeneity between supine and prone positions, stratified by body mass index (BMI). a) Ventilation improvement (percentage reduction in alveolar volume variance at peak inhalation) when moved from supine to prone is given for 31 patient-based lung structures, with b) a clear and statistically significant (*) ventilation improvement in obese compared with non-obese patients. c) Average inspiratory lung volume for 10 slices (from dorsal to ventral), with standard deviation of volumes, for high- and low-BMI patients. d) Ventilation maps in supine and prone positions in two patients. Brighter colours indicate increased ventilation. When moving from supine to prone, the low-BMI patient experiences a significant reversal in volume distribution, while the high-BMI patient experiences a flattening out of the volume distribution, suggesting reduced ventilation heterogeneity. Ventilation maps were created by calculating the average ventilation ratio per voxel, in an 80-80-80 grid overlaid on each structure. Each image is the average of 10 central voxels in the vertical axis.

similar Pearson's coefficients for males (0.64, p=0.026) and females (0.66, p=0.002). Similar ventilation improvements were seen in both asthmatics and healthy controls (figure 1a), suggesting that the effect was predominantly BMI-related.

Changes in ventilation when proned are further exhibited in the ventilation maps of the same high- and low-BMI patients (figure 1c and d). In a mid-lung transverse slice, ventilation distributions can be seen in supine and prone for both patients. The high-BMI patient achieves a much more even ventilation distribution in supine than prone, while the low-BMI patient does not, with proning leading to increased dorsal ventilation but reduced ventral ventilation.

Our observations using personalised computer models of lung ventilation would suggest that the benefits of proning begin in patients who are overweight and are most pronounced in obese patients with a BMI >30 kg·m^{-2}. These effects were seen for both asthmatic and healthy subjects and were independent of gender. We propose that patients with COVID-19 pneumonia who have concurrent obesity are encouraged to self-prone frequently during hospital admission and discharge to prevent potential progressive airway hypoventilation, closure and consequently pneumonia progression, requiring high flow respiratory support or mechanical ventilation.

The precise duration of self-proning needs to confirmed in clinical trials; however, observational data from case series in COVID-19 would suggest that as little as 5 min of proning can promote profound benefits in oxygenation, with protocols ranging 30–120 min being most beneficial [7].

On a practical note, the delivery of proning requires trained healthcare professionals *e.g.* physiotherapists capable of supporting the patient with optimal proning manoeuvres. In the case of the obese patient, this may include forward proning with wedged pillows and proning in the lateral decubitus position if full frontal proning is not technically feasible.

Our modelling approach has several limitations, including the static and non-time resolved nature of proning simulation, which precluded assessment of the impact of optimal proning duration on VH. Our models did not incorporate pulmonary perfusion, making assessment of the impact of pulmonary ventilation/perfusion distribution unfeasible. In addition, we did not generate models using CT scans from patients with COVID-19 pneumonia. Future modelling efforts will incorporate recently developed computational models of ventilation/perfusion [12] and time-resolved modelling using CT images from patients with varying severity levels of COVID-19 pneumonia.

In summary, we used computer models to demonstrate that proning is beneficial in obese patients, *via* reduced VH and improved ventilation in the lung. We speculate that the mechanical effects of obesity are a key factor of pneumonia progression in COVID-19 and that this risk may be reduced by effective self-proning strategies early in the disease course.

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