Intensive Care Medicine

LETTER Un-edited accepted proof

Physiological dead space ventilation, disease severity and outcome in ventilated patients with hypoxaemic respiratory failure due to Coronavirus Disease 2019

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Abbreviations: AHRF, COVID-19, ICU, PaO_2/FiO_2, CRP

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Dear Editor,

The severity of acute hypoxemic respiratory failure (AHRF) in COVID-19 correlates poorly with lung weight and lung mechanics, leading to the proposal of phenotypes that may be associated with similar degree of hypoxaemia but different lung volume, weight and compliance[1]. The alteration of the pulmonary vascular tone and immune-thrombosis of the alveolar capillaries[2] may account for these pathophysiological characteristics and for the high physiological dead space observed in these patients.

To describe estimated indices of physiological dead space - and their association with respiratory mechanics, severity of hypoxaemia, biomarkers and outcomes - we performed a retrospective analysis of adult patients with COVID-19 respiratory failure requiring mechanical ventilation in four medical Intensive Care Units (ICU) within Guy's & St Thomas' NHS Trust – London-UK (Ethics reference: 10796). We used the recorded values at the time of worst PaO_2/FiO_2 observed on the day of critical care admission. Continuous variables were compared using Mann-Whitney U test. This cohort included 213 patients (73% males) mean [95%CI] age 56 [54-57] years and PaO_2/FiO_2 128 [121-135] mmHg. When subdivided in four groups based on cut-off PaO_2/FiO_2 of 150 mmHg and compliance of 40 mL/cmH_2O; 72% (n=154) had PaO_2/FiO_2 <150mmHg, of these 112 (73%, or 53% of the overall cohort) had compliance <40 mL/cmH_2O (eTable 1). The mean [95%CI] estimated physiological dead space fraction[3] was high in the entire cohort at 0.53 [0.51-0.56].

ICU outcome was available for 193 patients, where estimated physiological dead space fraction was higher in non-survivors (median [IQR], 0.57 [0.46-0.65] vs 0.5 [0.4-0.64]; p=0.03). All estimates of physiological dead space increased with the degree of hypoxaemia, but not with the reduction in lung compliance (Figure 1). Compared with patients with PaO_2/FiO_2 >150mmHg, patients with PaO_2/FiO_2 <150mmHg had higher estimated physiological dead space fraction (0.55 [0.52-0.57] vs 0.50 [0.47-0.53]; p=0.036) (Figure 1A), mean [95%CI] corrected minute volume[4] (9.3 [8.8-9.7] vs 8.2 [7.6-8.8] L/min; p=0.004) (Figure 1B), and ventilatory ratio[5] (1.43 [1.37-1.50) vs 1.29 [1.20-1.38]; p=0.001)

(Figure 1C). Although patients with compliance <40 mL/cmH_2O had a higher corrected minute volume[4] (9.4 [8.8-10] vs 8.8 [8.4-9.3] L/min; p=0.023) (Figure 1C), there was no difference in the two compliance groups in estimated physiological dead space fraction (0.55 [0.48-0.56] vs 0.54 [0.52-0.56]; p=0.72) (Figure 1A) and ventilatory ratio[5] 1.4 [1.3-1.5) vs 1.4 [1.33-1.46]; p=0.76) (Figure 1B). Physiological dead space correlated with hypoxaemia, but it was dissociated from alterations in lung mechanics in COVID-19 ventilated patients. Immuno-thrombosis is a mechanism that may explain both the increase in physiological dead space and hypoxaemia. Interestingly, we found that the highest median [IQR] levels of D-Dimers (2.1 [1-7] mg/L); ferritin (1,627 [914 to 2,555] ug/L), CRP (219.5 [147.25, 324] mg/L), and troponin (23 [12-62]ng/L) were seen in patients with PaO_2/FiO_2 <150mmHg, but relatively preserved compliance (>40 mL/cmH_2O). However, these values were statistically similar to the ones recorded in the other groups.

In conclusion, these data suggest that increased physiological dead space is a characteristic of patients with COVID-19 AHRF, with no relation with compliance of the respiratory system. Given that both PaO_2/FiO_2 and physiological dead space are worse in non-survivors, it is unclear if dead space is independently associated with mortality or if its effect on outcome are mediated through hypoxaemia.

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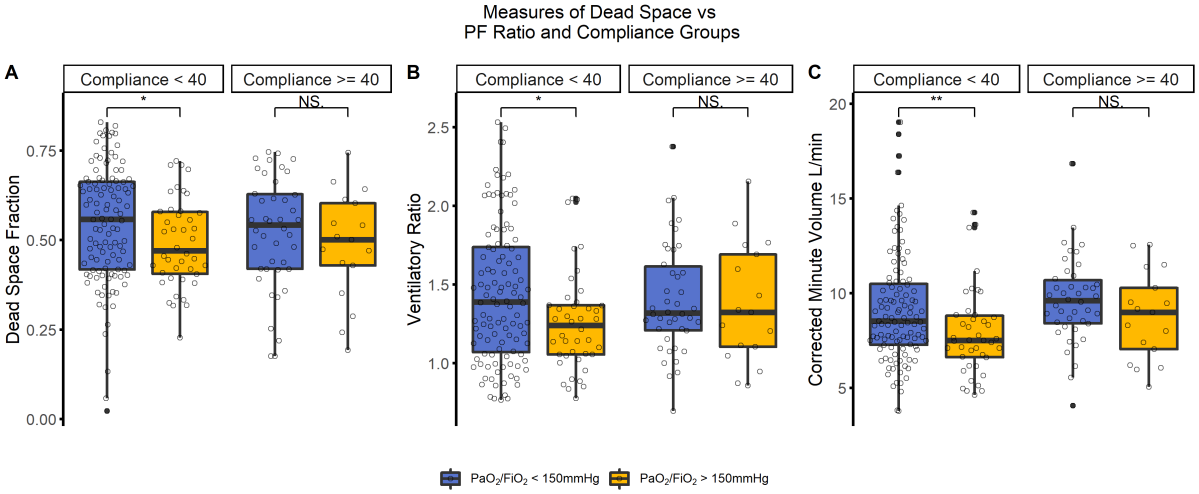
Figure 1: Distributions of dead space indices in the groups of compliance and PaO_2/FiO_2. A: Physiological dead space Fraction; B: Ventilatory Ratio; C: Corrected minute ventilation.



eTable 1: Distribution of patients based on categories of compliance and PaO_2/FiO_2

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	$PaO_2/FiO_2 \leq 150$mmHg		**$PaO_2/FiO_2 > 150$mmHg**	
n (%)	154 (72.3)		59 (27.7)	
PaO_2/FiO_2, mmHg mean(95% CI)	103 (98 – 107)		194 (185 – 204)	
Compliance ml/cmH_2O mean(95% CI)	33.3 (31.0 – 35.6)		35.3 (31.5 - 39.1)	
	Compliance < 40 cmH_2O	Compliance ≥ 40 cmH_2O	Compliance < 40 cmH_2O	Compliance ≥ 40 cmH_2O
n (%)[cohort %]	112 (72.7)[52.6]	42 (27.3)[19.7]	42 (71.2)[19.7]	17 (28.8)[8]
PaO_2/FiO_2, mmHg mean(95% CI)	102 (97 - 107)	105 (97 – 114)	186 (176 – 197)	213 (193 – 233)
Compliance ml/cmH_2O mean(95% CI)	26.2 (24.9 - 27.4)	52.2 (48.5 – 55.9)	27.8 (25.5 – 30.0)	53.9 (48.1 – 59.8)