J Crit Care 77 (2023) 154313

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Relationship between D-dimers and dead-space on disease severity and mortality in COVID-19 acute respiratory distress syndrome: A retrospective observational cohort study

Luigi Camporota, MD [a,b], Barnaby Sanderson, MD [a], Stephanie Worrall, MD [a], Marlies Ostermann, MD [a], Nicholas A. Barrett, MD [a], Andrew Retter, MD [a], Mattia Busana, MD [c], Patrick Collins, MD [a], Federica Romitti, MD [c], Beverley J. Hunt, MD [a], Louise Rose, MD [a,d], Luciano Gattinoni, MD [c], Davide Chiumello, MD [e,*]

[a] Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London SE1 7EH, UK
[b] Centre of Human Applied Physiological Sciences, King's College London, London, UK
[c] Department of Anesthesiology, University Medical Center of Göttingen, Germany
[d] Florence Nightingale Faculty of Nursing, Midwifery and Palliative Care, King's College London, London, UK
[e] Department of Anesthesiology and Intensive Care, ASST Santi e Paolo Hospital, University of Milan, Italy

ARTICLE INFO

Keywords:
Adult
Coronavirus disease 2019
Intensive care units
Respiratory distress syndrome

ABSTRACT

Background: Despite its diagnostic and prognostic importance, physiologic dead space fraction is not included in the current ARDS definition or severity classification. ARDS caused by COVID-19 (C-ARDS) is characterized by increased physiologic dead space fraction and hypoxemia. Our aim was to investigate the relationship between dead space indices, markers of inflammation, immunothrombosis, severity and intensive care unit (ICU) mortality.

Results: Retrospective data including demographics, gas exchange, ventilatory parameters, and respiratory mechanics in the first 24 h of invasive ventilation. Plasma concentrations of D-dimers and ferritin were not significantly different across C-ARDS severity categories. Weak relationships were found between D-dimers and VR ($r = 0.07$, $p = 0.13$), $P_{ET}CO_2/PaCO_2$ ($r = -0.1$, $p = 0.02$), or estimated dead space fraction ($r = 0.019$, $p = 0.68$). Age, PaO_2/FiO_2, pH, $P_{ET}CO_2/PaCO_2$ and ferritin, were independently associated with ICU mortality. We found no association between D-dimers or ferritin and any dead-space indices adjusting for PaO_2/FiO_2, days of ventilation, tidal volume, and respiratory system compliance.

Conclusions: We report no association between dead space and inflammatory markers in mechanically ventilated patients with C-ARDS. Our results support theories suggesting that multiple mechanisms, in addition to immunothrombosis, play a role in the pathophysiology of respiratory failure and degree of dead space in C-ARDS.

1. Background

Acute respiratory distress syndrome (ARDS) is characterized physiologically by a decrease in lung volumes and an increase in venous admixture and physiologic dead space fraction. Together this results in hypoxaemia and impaired carbon dioxide (CO_2) elimination [1]. ARDS severity is defined on the basis of PaO_2/FiO_2 ratio [1] - an index that correlates with the amount of non-aerated lung and with mortality [1,2]. Physiologic dead space fraction is an important index of overall lung function [3] that is strongly associated with more severe disease and

Abbreviations: ARDS, acute respiratory distress syndrome; CO_2, carbon dioxide; PaO_2, arterial oxygen partial pressure; FiO_2, inspired oxygen fraction; COVID-19, coronavirus disease 19; C-ARDS, ARDS caused by COVID-19; $PaCO_2$, arterial carbon dioxide partial pressure; $PvCO_2$, venous carbon dioxide partial pressure; ICU, intensive care unit; RT-PCR, reverse transcriptase polymerase chain reaction; APACHE II, acute physiology and chronic health evaluation II; SAPS II, simplified acute physiology score II; VE, minute ventilation; Vt, tidal volume; P_ETCO_2, end-tidal CO_2; BMI, body mass index; PEEP, positive end-expiratory pressure; SOFA, sequential organ failure assestment; VR, ventilatory ratio; PBW, predicted body weight..

* Corresponding author at: Department of Anesthesia and Intensive Care, ASST Santi Paolo e Carlo, San Paolo University Hospital, Via Di Rudini 9 Milan, Italy.
E-mail address: davide.chiumello@unimi.it (D. Chiumello).

https://doi.org/10.1016/j.jcrc.2023.154313

Available online 26 April 2023

lower survival in invasively ventilated patients with ARDS [4-6]. Despite its diagnostic and prognostic importance, physiologic dead space fraction is not included in the current ARDS definition or severity classification. Moreover, it is not routinely measured or reported in ARDS trials.

More recently, several reports document that ARDS caused by COVID-19 (C-ARDS) is characterized by increased physiologic dead space fraction [7] and hypoxemia. Yet the latter does not always correlate with the amount of non-aerated lung and therefore respiratory system compliance [8]. One possible explanation for this lack of correlation is that, in C-ARDS, the primary injury occurs at capillary endothelial level [9]. This leads to decreased perfusion of normally aerated lung (dead space) due to vasoconstriction and microvascular thrombosis also known as immunothrombosis [10,11]. In addition, the increased perfusion of non-aerated lung due to blood flow diversion and neoangiogenesis [12] in non-ventilated lung tissue (leading to venous admixture) increases the arterial tension of carbon dioxide ($PaCO_2$) [12]. Therefore, based, on the Riley's model of gas exchange [13] $PaCO_2$ (and calculated dead space) depends on the amount of non-aerated lung tissue and on the tension of CO_2 in the mixed venous blood ($PvCO_2$).

The evidence of decreased perfusion of ventilated lung regions in the absence of thrombosis comes from small studies [10,14] with ventilation/perfusion mismatch resulting from dysregulated vascular tone. The more prevalent mechanism leading to increase in ventilation/perfusion ratio is vascular thrombosis. In C-ARDS, the extent of immunothrombosis and the plasma levels of markers such as D-Dimers and ferritin, have been associated with increased disease severity and mortality [15,16]. However, the relationship between immunmothrombosis of pulmonary vessels and indices of dead space on mortality has yet to be demonstrated or quantified.

Therefore, our aim was to investigate the relationship of dead space indices and inflammatory markers (ferritin and D-dimers) on C-ARDS severity and intensive care unit (ICU) mortality in a large cohort of patients receiving mechanical ventilation for C-ARDS.

2. Methods

2.1. Study population

We included consecutive adults (>18 years) with C-ARDS from two centres (San Paolo Milan - Italy; Guy's & St Thomas' Hospital NHS Foundation Trust, London, UK) from March 2020 to March 2021. All patients fulfilled the Berlin ARDS definition [1] and C-ARDS, with documented COVID-19 positive reverse transcriptase polymerase chain reaction (RT-PCR) results from an upper airway swab or bronchoalveolar lavage. This retrospective study was registered at GSTT in UK as a service evaluation (number 10796) with a waiver of consent for the use of anonymized retrospective data accrued though provision of routine clinical services. In Italy, the study was approved by local ethical committee (Comitato Etico Interaziendale Milano Area *A*1, n. 628). All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975. Data were anonymised locally before entry into the central database.

2.2. Measurements

We collected data retrospectively from electronic patient records, including demographics, Acute Physiology and Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology Score (SAPS) II severity scores, gas exchange, ventilatory parameters, and respiratory mechanics. We documented the worst value of these parameters in the first 24 h of invasive ventilation. We calculated PaO_2/FiO_2 ratio, minute volume (VE), tidal volume (V_T) per predicted body weight, ventilatory ratio [17], corrected minute volumes [18] and estimated dead space [19]. From raw data we calculated driving pressure (plateau pressure minus PEEP, or tidal volume divided by compliance of the respiratory system) [20], respiratory system compliance and mechanical power [21] and end-tidal$Co_2/PaCO_2$ ratio ($P_{ET}CO_2/PaCO_2$). To calculate mechanical power, we used the simplified formula described by Becher et al [22], given the heterogeneity of ventilation modes and limited availability of inspiratory time data. We collected parameters required for APACHE II and SAPS II scores, and documented days of invasive ventilation and ICU mortality.

2.3. Statistical analysis

We report categorical data as counts and percentages, continuous data as median and interquartile ranges (IQR) or 95% confidence intervals. We examined data distribution of continuous variables using Shapiro-Wilk tests. For non-parametric comparisons we used Mann-Whitney U or Kruskal Wallis tests. Differences in paired measurements were examined with Wilcoxon signed rank tests. Between-group differences of categorical data was examined using Pearson's χ^2 test. To evaluate the association between two variables we used Pearson's or Spearman correlation. We constructed multivariable linear regression models of variables related to indices of dead-space and a logistic regression model for mortality using variables that demonstrated significance in univariable logistic regression. Linear regression models were used to describe the relationship between continuous variables including relationship with BMI. A *P* value of 0.05 was considered significant. All analyses were performed using STATA (StataCorp, Texas, USA) v.17.0.

3. Results

3.1. Patient characteristics

We included data from 557 invasively mechanically ventilated patients with C-ARDS. Patients were enrolled in the study after a median [IQR] of 1 [0–9] days from admission to ICU. We report patient

Table 1
Demographics.

Variable	Median	IQR
Gender, male (%)	70%	
Age, years	59	51–66
BMI, Kg/m^2	27.8	24.5–33.1
SOFA	5	4–7
Tidal volume, ml	462	400–520
Tidal volume/PBW, ml	7.0	6.0–7.9
Respiratory rate, breaths/min	18	16–21
Minute ventilation, L/min	8.0	6.5–9.6
FiO_2,	60	50–80
Airway Peak pressure, cmH_2O	26	23–29
Airway Plateau pressure, cmH_2O	25	22–28
PEEP, cmH_2O	10	8–12
Driving pressure, cmH_2O	14	10–17
pH	7.4	7.3–7.4
$PaCO_2$, mmHg	44.3	38.6–50.5
PaO_2, mmHg	67.5	60.9–77.6
$P_{ET}CO_2$, mmHg	34.5	30–40.5
Minute ventilation corrected, L/min	9.2	7.3–11.5
Ventilatory Ratio	1.4	1.1–1.8
Estimated dead-space	0.5	0.4–0.6
$P_{ET}CO_2/PaCO_2$ ratio	0.79	0.69–0.89
PaO_2/FiO_2	108.1	86.0–143.6
Compliance, mL/cmH_2O	32.8	25.3–44.6
Mechanical Power, J/min	15.1	11.4–19.8
D-Dimers μg/L	1850	850–6010
Ferritin μg/L	1059	587–1995
ICU mortality (%)	33.4	

BMI denotes body mass index, SOFA the Sequential Organ Failure Assessment score, PWB predicted body weight, FiO2 the fraction of inspired oxygen, PEEP positive end expiratory pressure, PaCO2 the partial pressure of arterial carbon dioxide, PaO2 the partial pressure of arterial oxygen, $P_{ET}CO2$ the end tidal partial pressure of carbon dioxide.

characteristics, baseline ventilation and gas exchange in Table 1. Most were male (70%), had moderate (52%) or severe (40%) C-ARDS (PaO_2/FiO_2 ratio at clinical PEEP [1]); 37% were obese (body mass index (BMI) >30 Kg/m^2). SOFA score and BMI increased across C-ARDS severity categories. Patients in all three C-ARDS severity groups had almost identical respiratory system compliance despite statistically significant differences in PaO_2/FiO_2 ratio and dead space indices.

3.2. Characteristics based on C-ARDS severity

3.2.1. Ventilation settings

Patients were ventilated in pressure-controlled (84%) or volume-controlled modes (16%). At baseline, ventilation was applied using traditional lung protective ventilation criteria with median [IQR] V_T of 7 [6.0–7.9] ml/Kg predicted body weight, driving pressure of 14 [10–17] cmH_2O, and mechanical power of 15.1 [11.4–19.8] J/min.

V_T, VE and driving pressure were similar among all C-ARDS severity categories. Mechanical power increased from 11.6 [9.4–16.1] J/min in mild C-ARDS, to 16.1 [12.2–22.1] J/min in severe C-ARDS, ($p < 0.001$), mainly due to increasing respiratory frequency and PEEP across C-ARDS severity (Table 3).

We found a statistically significant relationship between increasing BMI and clinician set PEEP ($r = 0.27$; $p < 0.0001$) and an inverse relationship to PaO_2/FiO_2 ratio ($r = -0.16$; $p < 0.0001$). Increasing BMI also was associated with worse physiological dead space and ventilatory ratio (VR) ($r = 0.15$; $p < 0.0001$).

3.2.2. Dead space indices

Eighty-five percent of patients had a VR >1; and 89.4% had a $P_{ET}CO_2/PaCO_2$ ratio < 1 indicating increased dead space is highly prevalent in C-ARDS. Despite similar $PaCO_2$, all dead space indices worsened as C-ARDS severity increased (Table 3). Specifically, VR and VE-corrected increased. VR increased from a median (IQR) of 1.32 (1.08–1.65) in mild C-ARDS to 1.46 (1.16–1.88) in severe C-ARDS ($p = 0.013$) VE-corrected increased from 8.2 L/min (6.6–10.1) in mild C-ARDS to 9.6 L/min (7.7 to 11.9) in severe C-ARDS($p = 0.016$). $P_{ET}CO_2/PaCO_2$ ratio progressively decreased from a median (IQR) of 0.87 (0.79–0.98) in mild C-ARDS to 0.76 (0.64–0.86) in severe C-ARDS ($p < 0.001$) widening the $PaCO_2$-$P_{ET}CO_2$difference ($p < 0.001$) (Table 3). $P_{ET}CO_2/PaCO_2$ was inversely associated with days of mechanical ventilation ($p = 0.047$), i.e., $P_{ET}CO_2/PaCO_2$ decreased over time.

In our linear regression models, VR and $P_{ET}CO_2/PaCO_2$ were significantly associated with PaO_2/FiO_2 ratio and respiratory system compliance, although no relationship was found between PaO_2/FiO_2 ratio and respiratory system compliance.

3.2.3. Dead space indices and markers of immunothrombosis

Plasma concentrations of D-dimers and ferritin were not significantly different across C-ARDS severity categories. Only weak relationships were found between D-dimers and VE-corrected ($r = 0.11$, $p = 0.012$), $P_{ET}CO_2/PaCO_2$ ($r = -0.1$, $p = 0.02$), VR ($r = 0.07$, $p = 0.13$), or estimated dead space fraction ($r = 0.019$, $p = 0.68$). Our multivariable linear regression model found no association between D-dimers or ferritin and any dead-space indices adjusting for PaO_2/FiO_2, days of ventilation, V_T, and respiratory system compliance.

3.3. Mortality

The overall cohort ICU mortality was 33%, which increased across C-ARDS severity categories (mild = 18%; moderate =30%; and severe = 41%, $p = 0.004$). Non-survivors were older and had lower BMI (Table 2). Admission SOFA scores were similar between survivors and non-survivors. Despite similar baseline respiratory system compliance, non-survivors were ventilated with higher V_T (7.4 [6.1, 8.2] vs 6.8 [6.0, 7.8] ml/Kg PBW; $p = 0.008$) and mechanical power. Non-survivors had worse oxygenation and worse dead space ventilation indices (Table 2). Of the 369 patients with ferritin levels measured at baseline, 39% had ferritin >1500 (μg/L). Median (IQR) ferritin was higher in non-survivors (1271 [718, 2607] vs 1008 [577, 1868]; $p = 0.017$). Of the 474 patients with D-dimers measured, 30% had D-dimers levels >4000 (μg/L). There

Table 2
Demographics by Outcome (ICU Mortality).

	Survivors			Non-Survivors			
Variable	Median	IQR		Median	IQR		p
Gender, males (%)	67.7			74.7			0.090
Age, years	57.0	49.0	63.0	62.0	57.0	69.0	<0.001
BMI, Kg/m^2	28.0	24.5	34.3	27.2	24.5	30.9	0.008
SOFA	5.0	4.0	7.0	6.0	4.0	8.0	0.140
Tidal Volume, ml	456.0	399.0	507.0	480.0	401.0	550.0	0.043
Tidal Volume/PBW, ml	6.8	6.0	7.8	7.4	6.1	8.2	0.008
Respiratory Rate, breaths/min	18.0	16.0	21.0	18.0	16.0	22.0	0.900
Minute ventilation, L/min	8.0	6.5	9.4	8.2	6.7	9.8	0.090
FiO_2 (%)	60.0	45.0	70.0	70.0	55.0	80.0	<0.001
Airway Peak Pressure, cmH_2O	26.0	22.0	29.0	27.0	24.0	30.0	0.003
Airway Plateau Pressure, cmH_2O	25.0	21.0	28.0	25.0	22.0	28.0	0.600
PEEP, cmH_2O	10.0	8.0	12.0	10.0	8.0	12.0	0.020
Driving Pressure, cmH_2O	14.00	11.00	17.00	13.00	10.00	17.00	0.230
pH	7.39	7.34	7.43	7.36	7.31	7.41	<0.001
$PaCO_2$, mmHg	43.5	37.9	49.6	46.0	40.0	52.9	0.004
PaO_2, mmHg	68.1	61.1	77.9	67.1	60.8	76.7	0.550
$P_{ET}CO2$ $_2$, mmHg	35.3	30.8	41.3	33.8	28.5	39.8	0.020
Minute Ventilation Corrected, L/min	8.8	7.1	11.3	9.9	7.8	12.1	0.004
Ventilatory Ratio	1.3	1.1	1.7	1.6	1.3	1.9	<0.001
Estimated Dead-Space	0.52	0.39	0.62	0.59	0.47	0.66	<0.001
$P_{ET}CO_2/PaCO_2$ ratio	0.81	0.71	0.92	0.74	0.64	0.84	<0.001
PaO_2/FiO_2, mmHg	117.4	89.9	151.3	100.2	80.9	123.0	<0.001
Compliance, mL/cmH_2O	32.1	25.3	43.6	34.3	25.0	48.0	0.180
Mechanical Power, J/min	14.3	11.2	18.6	16.9	11.9	21.9	0.001
D-Dimers μg/L	1795.0	815.0	5448.5	1885.0	930.0	7320.0	0.320
Ferritin μg/L	1008.5	577.5	1868.0	1271.0	718.0	2607.0	0.017

BMI denotes body mass index, SOFA the Sequential Organ Failure Assessment score, PWB predicted body weight, FiO2 the fraction of inspired oxygen, PEEP positive end expiratory pressure, PaCO2 the partial pressure of arterial carbon dioxide, PaO2 the partial pressure of arterial oxygen, $P_{ET}CO2$ the end tidal partial pressure of carbon dioxide.

was no difference in D-dimers levels between survivors and non-survivors (Table 2).

Multivariable logistic regression found that age, PaO_2/FiO_2, pH, $P_{ET}CO_2/PaCO_2$ and ferritin, were independently associated with ICU mortality (Table 3). Other dead-space indices (estimated physiological dead-space, minute volume corrected and VR) were associated with mortality in univariable analysis but not once adjusted in a multivariable analysis.

4. Discussion

4.1. Key findings

This multicentre cohort study examined the relationship between dead space and inflammatory markers - generally seen as markers of immunothrombosis - in mechanically ventilated patients with C-ARDS; and further evaluated the correlations between these variables, and association with C-ARDS severity and ICU mortality.

We confirmed that increased dead space ventilation is highly prevalent in C-ARDS and worsens with disease severity. Similarly, elevated inflammatory markers are common and associated with increased ICU mortality. Importantly, we demonstrated no correlation between dead space indices and inflammatory markers when accounting for confounding factors influencing dead space. Our second major finding was that D-dimer and ferritin, $P_{ET}CO_2/PaCO_2$, and PaO_2/FiO_2 were independent predictors of ICU mortality.

Our results further support data from other studies describing increased dead space ventilation in C-ARDS. Yet we found no relationship between dead space and inflammatory markers in contrast to a small number of reports describing a positive association between D-dimer and dead space [16,23,24]. The specific underlying mechanism for increased dead space ventilation – particularly the relationship with immunothrombosis - has yet to be fully established [8,25]. Pulmonary vascular endothelial dysfunction, micro thrombosis and angiogenesis resulting from immune and coagulation dysregulation remain the prevailing hypotheses [12,26] supported by biochemical, pathological, and radiographical evidence. Furthermore, autopsy studies of those who have died from COVID-19 pneumonia in the first waves have described pulmonary vascular endothelial injury and microthrombi [12,27-29]. Imaging studies indicate areas of hypoperfusion in keeping with pulmonary micro and macro vascular thrombosis [10,11,16,30-35]. There is no clear biomarker of immunothrombosis and we hypothesized that ferritin and D-dimers, which are very elevated in COVID-19 pneumonia patients might be potential biomarkers in this patient group. However D-dimers are very high in all cases of ARDS and may reflect increased fibrinolysis within the lungs due to the local production of urokinase by pneumocytes in response to local fibrin deposition [36]. Our study shows there is no relationship between these inflammatory biomarkers and dead space.

Earlier studies demonstrate heterogeneity in the dead space surrogates used, and in all only a single surrogate was used to quantify dead space. In this study, we measured multiple dead space indices and used linear regression analysis to account for confounding factors specific to dead space. For example, an early case series of four patients receiving mechanical ventilation for C-ARDS observed a simultaneous rise in dead space ventilation and D-dimer which occurred early-on in the ICU admission and preceding hypercapnia [24]. Grasselli et al. reported a positive correlation between D-dimer and VR in 301 mechanically-ventilated patients with C-ARDS [16], whilst Bhatt et al. found D-dimer >2000 μg/dL was associated with increased dead space.

Our results add to the current hypothesis that increased dead space ventilation in C-ARDS results from multiple compounding pathophysiological mechanisms, the net effect of which is reduced perfusion to aerated lung tissue. Possible mechanisms include immunothrombosis, lung parenchymal damage and over-inflation resulting in capillary collapse similar to that observed in classical ARDS [6,37-39]; and dysregulation in pulmonary vascular tone and loss of hypoxic vasoconstriction [8,40-42] or opening of anastomosis between pulmonary arteries and bronchial vasculature – which can increase in patients with COVID-19 disease. The creation of such anastomoses and the dilated bronchial microvasculature leads to potential right-to-left shunts, bypassing the alveolar-capillary network [43]. These changes can potentially explain why some indices of dead-space are more associated with oxygenation (also affected by bronchial shunts) than with compliance or inflammatory markers. Furthermore, COVID-19 is a systemic disorder with SARS-CoV-2 detected at multiple extrapulmonary sites including the kidneys, heart, liver, and brain [44-46]. Therefore, systemic extra-pulmonary inflammation is a plausible explanation for increased levels of inflammatory markers independent of the severity of physiological dead space.

4.1.1. Clinical implications

Our results add to a considerable evidence base describing an association between dead space ventilation, disease severity and mortality in C- ARDS [25,35,37,38,47] but do not support the role of inflammation as the main determinant of physiological dead space.

Severe COVID-19 has increased risk of thrombotic complications resulting in research directed at establishing optimal preventative strategies [48,49]. Current guidelines advise standard weight-adjusted thromboprophylaxis with low molecular weight heparin in ICU patients with C-ARDS and escalation to treatment-dose only in cases of established thromboembolic disease [50].

4.1.2. Strengths and limitations

This study is one the first to evaluate the relationship between dead space ventilation and inflammatory markers in C-ARDS using multiple dead space indices addressing existing heterogeneity in dead space measurements across previous studies. We also used linear regression analysis to account for confounding factors. The main strength of this study was the international, multicentre methodology recruiting patients over an extensive study period, increasing external validity. However, our study has limitations. First, our linear regression model did not account for all factors that may influence dead space ventilation in C-ARDS. An additional model including variables that influence levels of inflammatory markers could have improved data validity. Second, data collection and analysis were retrospective, leading to missing biochemical and radiological data, and no data on anticoagulation or renin and angiotensin data – as not collected in routine clinical practice. Inclusion of computerised tomography (CT) scans and data on anticoagulation would have facilitated discussion about the role of thrombosis in the aetiology of increased dead space ventilation in C-ARDS.

Table 3
Factors associated with ICU mortality.

Variables	Odds Ratio	[95% Conf.	Interval]	P
Age	1.062	1.033	1.090	<0.0001
PaO_2/FiO_2 (mmHg)	0.990	0.981	0.995	0.002
$P_{ET}CO_2/PaCO_2$ (mmHg)	0.171	0.032	0.92	0.040
pH	0.015	0.0004	0.54	0.022
Ferritin (μg/L)	1.221	1.082	1.377	0.001

PaO2/FiO2 the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, $P_{ET}CO_2/PaCO_2$ the ratio of end tidal to arterial partial pressure of carbon dioxide.

5. Conclusions

In this international, multicentre, cohort study we report no association between dead space and inflammatory markers in mechanically ventilated patients with C- ARDS. Our results support theories suggesting that multiple mechanisms, in addition to immunothrombosis, play a role in the pathophysiology of respiratory failure and degree of dead space in C-ARDS. Further research is necessary to elucidate the specific

pathogenesis of increased dead space in C-ARDS to facilitate the development of targeted therapies.

Ethics approval and consent to participate

This retrospective study was registered at GSTT in UK as a service evaluation (number 10796) with a waiver of consent for the use of anonymized retrospective data accrued though provision of routine clinical services. In Italy, the study was approved by local ethical committee (Comitato Etico Interaziendale Milano Area *A*1, n. 628). All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

Consent for publication

Not applicable;

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request;

Funding

Not applicable;

Author's contribution

L.C., L.G. and D.C. conceptualization and writing the first draft of the manuscript; B.S., S.W., M.O., N.B., A.R., M.B., P.C., F.R., B.H. and L.R. retrieved the data; M.B. performed the analysis; L.C., M.B., F.R., L.C. and D.C. revised the initial version of the manuscript.

Financial disclosures

The authors have no financial relationship to disclose in relation to the writing of this manuscript.

CRediT authorship contribution statement

Luigi Camporota: Conceptualization, Supervision, Writing – original draft. **Barnaby Sanderson:** Formal analysis, Investigation, Methodology, Software, Visualization. **Stephanie Worrall:** Data curation, Methodology, Writing – review & editing. **Marlies Ostermann:** Data curation, Methodology, Writing – review & editing. **Nicholas A. Barrett:** Data curation, Methodology, Writing – review & editing. **Andrew Retter:** Data curation, Methodology, Writing – review & editing. **Mattia Busana:** Data curation, Methodology, Writing – review & editing. **Patrick Collins:** Data curation, Methodology, Writing – review & editing. **Federica Romitti:** Data curation, Methodology, Writing – review & editing. **Beverley J. Hunt:** Data curation, Methodology, Writing – review & editing. **Louise Rose:** Data curation, Methodology, Writing – review & editing. **Luciano Gattinoni:** Methodology, Supervision, Writing – review & editing. **Davide Chiumello:** Methodology, Supervision, Writing – original draft.

Declaration of Competing Interest

The authors declare no conflicts of interest in writing this manuscript.

Acknowledgments

Not applicable.

References

[1] Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307(23):2526–33.
[2] Reske AW, Costa EL, Reske AP, et al. Bedside estimation of nonaerated lung tissue using blood gas analysis. Crit. Care Med. 2013;41(3):732–43.
[3] Bonifazi M, Romitti F, Busana M, et al. End-tidal to arterial PCO2 ratio: a bedside meter of the overall gas exchanger performance. Intensive Care Med. Exp. 2021;9(1):21.
[4] Cepkova M, Kapur V, Ren X, et al. Pulmonary dead space fraction and pulmonary artery systolic pressure as early predictors of clinical outcome in acute lung injury. Chest 2007;132(3):836–42.
[5] Raurich JM, Vilar M, Colomar A, et al. Prognostic value of the pulmonary dead-space fraction during the early and intermediate phases of acute respiratory distress syndrome. Respir. Care 2010;55(3):282–7.
[6] Nuckton TJ, Alonso JA, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N. Engl. J. Med. 2002;346(17):1281–6.
[7] Vasques F, Sanderson B, Formenti F, et al. Physiological dead space ventilation, disease severity and outcome in ventilated patients with hypoxaemic respiratory failure due to coronavirus disease 2019. Intensive Care Med. 2020;46(11):2092–3.
[8] Chiumello D, Busana M, Coppola S, et al. Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: a matched cohort study. Intensive Care Med. 2020;46(12):2187–96.
[9] Flaumenhaft R, Enjyoji K, Schmaier AA. Vasculopathy in COVID-19. Blood 2022;140(3):222–35.
[10] Santamarina MG, Boisier Riscal D, Beddings I, et al. COVID-19: what iodine maps from perfusion CT can reveal-A prospective cohort study. Crit. Care 2020;24(1):619.
[11] Santamarina MG, Boisier D, Contreras R, et al. COVID-19: a hypothesis regarding the ventilation-perfusion mismatch. Crit. Care 2020;24(1):395.
[12] Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in covid-19. N. Engl. J. Med. 2020;383(2):120–8.
[13] Riley RL, Cournand A. Ideal alveolar air and the analysis of ventilation-perfusion relationships in the lungs. J. Appl. Physiol. 1949;1(12):825–47.
[14] Mak SM, Mak D, Hodson D, et al. Pulmonary ischaemia without pulmonary arterial thrombus in COVID-19 patients receiving extracorporeal membrane oxygenation: a cohort study. Clin. Radiol. 2020;75(10):795. e791-795 e795.
[15] Short SAP, Gupta S, Brenner SK, et al. D-dimer and death in critically ill patients with coronavirus disease 2019. Crit. Care Med. 2021;49(5):e500–11.
[16] Grasselli G, Tonetti T, Protti A, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir. Med. 2020;8(12):1201–8.
[17] Sinha P, Fauvel NJ, Singh S, et al. Ventilatory ratio: a simple bedside measure of ventilation. Br. J. Anaesth. 2009;102(5):692–7.
[18] Wexler HR, Lok P. A simple formula for adjusting arterial carbon dioxide tension. Can. Anaesth. Soc. J. 1981;28(4):370–2.
[19] Beitler JR, Thompson BT, Matthay MA, et al. Estimating dead-space fraction for secondary analyses of acute respiratory distress syndrome clinical trials. Crit. Care Med. 2015;43(5):1026–35.
[20] Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. N. Engl. J. Med. 2015;372(8):747–55.
[21] Gattinoni L, Tonetti T, Cressoni M, et al. Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med. 2016;42(10):1567–75.
[22] Becher T, Adelmeier A, Frerichs I, et al. Adaptive mechanical ventilation with automated minimization of mechanical power-a pilot randomized cross-over study. Crit. Care 2019;23(1):338.
[23] Bhatt A, Deshwal H, Luoma K, et al. Respiratory mechanics and association with inflammation in COVID-19-related ARDS. Respir. Care 2021;66(11):1673–83.
[24] Oppenheimer BW, Bakker J, Goldring RM, et al. Increased dead space ventilation and refractory hypercapnia in patients with coronavirus disease 2019: a potential marker of thrombosis in the pulmonary vasculature. Crit. Care Explor. 2020;2(9):e0208.
[25] Bertelli M, Fusina F, Prezioso C, et al. COVID-19 ARDS is characterized by increased dead space ventilation compared with non-COVID ARDS. Respir. Care 2021;66(9):1406–15.
[26] Poor HD, Ventetuolo CE, Tolbert T, et al. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfunction responsive to thrombolysis. Clin. Transl. Med. 2020;10(2):e44.
[27] Fox SE, Akmatbekov A, Harbert JL, et al. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir. Med. 2020;8(7):681–6.
[28] Nicolai L, Leunig A, Brambs S, et al. Immunothrombotic dysregulation in COVID-19 pneumonia is associated with respiratory failure and coagulopathy. Circulation 2020;142(12):1176–89.
[29] Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N. Engl. J. Med. 2020;382(17):e38.
[30] Grillet F, Busse-Cote A, Calame P, et al. COVID-19 pneumonia: microvascular disease revealed on pulmonary dual-energy computed tomography angiography. Quant. Imag. Med. Surg. 2020;10(9):1852–62.
[31] Patel BV, Arachchillage DJ, Ridge CA, et al. Pulmonary angiopathy in severe COVID-19: physiologic, imaging, and hematologic observations. Am. J. Respir. Crit. Care Med. 2020;202(5):690–9.
[32] Ramos CD, Fernandes AP, Souza SPM, et al. Simultaneous imaging of lung perfusion and glucose metabolism in COVID-19 pneumonia. Am. J. Respir. Crit. Care Med. 2021;203(9):1186–7.

[33] Ridge CA, Desai SR, Jeyin N, et al. Dual-energy CT pulmonary angiography (DECTPA) quantifies vasculopathy in severe COVID-19 pneumonia. Radiol. Cardiothorac. Imag. 2020;2(5):e200428.
[34] Lang C, Jaksch P, Hoda MA, et al. Lung transplantation for COVID-19-associated acute respiratory distress syndrome in a PCR-positive patient. Lancet Respir. Med. 2020;8(10):1057–60.
[35] Ball L, Robba C, Maiello L, et al. Computed tomography assessment of PEEP-induced alveolar recruitment in patients with severe COVID-19 pneumonia. Crit. Care 2021;25(1):81.
[36] Hunt BJ, Levi M. Re the source of elevated plasma D-dimer levels in COVID-19 infection. Br. J. Haematol. 2020;190(3):e133–4.
[37] Ospina-Tascon GA, Bautista DF, Madrinan HJ, et al. Microcirculatory dysfunction and dead-space ventilation in early ARDS: a hypothesis-generating observational study. Ann. Intensive Care 2020;10(1):35.
[38] Morales-Quinteros L, Schultz MJ, Bringue J, et al. Estimated dead space fraction and the ventilatory ratio are associated with mortality in early ARDS. Ann. Intensive Care 2019;9(1):128.
[39] Tomashefski Jr JF, Davies P, Boggis C, et al. The pulmonary vascular lesions of the adult respiratory distress syndrome. Am. J. Pathol. 1983;112(1):112–26.
[40] Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020;46(6):1099–102.
[41] Herrmann J, Mori V, Bates JHT, et al. Modeling lung perfusion abnormalities to explain early COVID-19 hypoxemia. Nat. Commun. 2020;11(1):4883.
[42] Busana M, Giosa L, Cressoni M, et al. The impact of ventilation-perfusion inequality in COVID-19: a computational model. J. Appl. Physiol. (1985) 2021;130(3):865–76.
[43] Galambos C, Bush D, Abman SH. Intrapulmonary bronchopulmonary anastomoses in COVID-19 respiratory failure. Eur. Respir. J. 2021;58(2).
[44] Robba C, Battaglini D, Ball L, et al. Coagulative disorders in critically ill COVID-19 patients with acute distress respiratory syndrome: a critical review. J. Clin. Med. 2021;10(1).
[45] Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395(10234):1417–8.
[46] Teuwen LA, Geldhof V, Pasut A, et al. COVID-19: the vasculature unleashed. Nat. Rev. Immunol. 2020;20(7):389–91.
[47] Diehl JL, Peron N, Chocron R, et al. Respiratory mechanics and gas exchanges in the early course of COVID-19 ARDS: a hypothesis-generating study. Ann. Intensive Care 2020;10(1):95.
[48] Merrill JT, Erkan D, Winakur J, et al. Emerging evidence of a COVID-19 thrombotic syndrome has treatment implications. Nat. Rev. Rheumatol. 2020;16(10):581–9.
[49] Loo J, Spittle DA, Newnham M. COVID-19, immunothrombosis and venous thromboembolism: biological mechanisms. Thorax 2021;76(4):412–20.
[50] NIH: COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/.