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Quantitative CT scan and response to pronation in COVID-19 ARDS

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Author Contributions

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Abstract

Background: The use of the prone position (PP) has been widespread during the COVID-19 pandemic. While it has demonstrated benefits, including improved oxygenation and lung aeration, the factors influencing the response in terms of gas exchange to PP remain unclear. In particular, the association between baseline quantitative Computed Tomography (qCT) scan results and gas exchange response to PP in intubated, mechanically ventilated subjects with COVID-19 ARDS is unknown. The present study aimed to compare baseline qCT results between subjects responding to PP in terms of oxygenation or carbon dioxide (CO_2) clearance and those who did not.

Methods: This was a single-center, retrospective observational study, including critically ill, intubated, mechanically ventilated subjects with COVID-19 related acute respiratory distress syndrome admitted to the ICUs of Niguarda Hospital between March 2020 and November 2021. Blood-gas samples were collected before and after PP. Subjects in whom the PaO_2/FiO_2 increase was ≥ 20 mmHg after PP were defined as Oxygen responders (Oxy-R). CO_2-responders (CO_2R) were defined when the ventilatory ratio (VR) decreased during PP. Automated qCT analyses were performed to obtain tissue mass and density of the lungs.

Results: One hundred twenty-five subjects were enrolled, of which 116 (93%) were Oxy-R and 51 (41%) CO_2R. No difference in qCT characteristics and oxygen were observed between Oxy-R and Oxygen Non Responders (Tissue mass 1532 ±396 vs. 1654 ±304 g, p= .28; density -544±109 vs. -562±58 HU, p= .42). Similar findings were observed when dividing the population according to CO_2 response (Tissue mass 1551±412 vs. 1534±377 g, p= .89; density -545±123 vs. -546±94 HU, p= .99).

Conclusions: Most COVID-19 related ARDS subjects improve their oxygenation at the first pronation cycle. The study suggests that baseline qCT scan data are not associated with the response to PP in oxygenation or CO_2 in mechanically ventilated COVID-19 related ARDS subjects.

Keywords: Computed Tomography Scanner, Quantitative CT scan analysis, Prone position, COVID-19 ARDS, Coronavirus Severe Acute Respiratory Syndrome, Pulmonary Gas Exchange, Lung compliance, Ventilation-Perfusion Scan

Introduction

Prone position (PP) has been extensively used during the COVID-19 pandemic in intubated, mechanically ventilated subjects[1]. The benefits reported from the use of this position in "classic" acute respiratory distress syndrome (ARDS) were also confirmed in COVID-19 associated ARDS[2]. This strategy, requiring highly trained personnel and not devoid of possible complications [3–5], has thus been included in the guidelines for the treatment of moderate and severe COVID-19 associated ARDS[6]. Indeed, while results from randomized controlled trials in this specific population are lacking, placing subjects with COVID-19 associated ARDS in PP decreases alveolar collapse, hyperinflation, and improves the homogeneity of lung aeration and ventilation[2,7]. Moreover, while not the primary target of PP, several studies reported a variable (*i.e.*, between 30 and 80%) improvement in oxygenation during PP of mechanically ventilated subjects with COVID-19 associated ARDS[1,2]. However, it is currently unknown which factors contribute to, and how to predict the response in terms of oxygenation in subjects with ARDS placed in PP.

Chest Computed Tomography (CT) was broadly used in COVID-19 subjects to facilitate diagnosis and quantify the degree of disease extension[8,9]. Several radiological patterns could be observed at different times throughout the disease course, showing diffuse lung alterations ranging from ground-glass opacities to parenchymal consolidations[10,11]. In addition, the quantitative CT (qCT) results, cornerstones for the understanding of classic ARDS[12], have been analyzed to investigate the pathophysiology of COVID-19 associated ARDS and the lung response to PP in selected groups of subjects[2,13]. Previous studies have suggested that in supine position, the amount of non-aerated lung tissue in the dependent lung regions was associated with more recruitable lung volume when PP was used[14–16], and recently, a relationship between the dorsal non-aerated tissue quantified at the CT scan and the gas exchange response to PP was recorded in classical ARDS[17]. These studies, however, did not focus on the association between qCT results and the oxygenation response to PP in COVID-19 related ARDS subjects.

Recently, Raimondi *et al*.[18] studied awake, non-invasively ventilated COVID-19 subjects and were not able to find any association between the distribution of CT lung lesions and the response in oxygenation to PP.

Information regarding the association of baseline qCT results and the response to PP in intubated, mechanically ventilated subjects with COVID-19 associated ARDS is currently lacking. We hypothesized that the qCT results of scans performed prior to the first PP would differ significantly between responders and non-responders in terms of oxygenation and carbon dioxide (CO_2) clearance. The present retrospective study was conducted to test this hypothesis.

Methods

Study design

This was a single-center, retrospective, observational study performed at the Grande Ospedale Metropolitano Niguarda in Milan, Italy. The retrospective access to clinical data was approved by the ethical committee Milano Area B (approval number: 593-06102020), and the need for informed consent from individual subjects was waived.

All subjects admitted between March 1st, 2020, and November 30th, 2021, to the COVID-19 ICUs were screened for eligibility. Inclusion criteria were as follows: (i) age above 18 years; (ii) laboratory-confirmed SARS-CoV-2 infection; (iii) ARDS diagnosis according to Berlin criteria at ICU admission[19]; (iv) tracheal intubation and invasive mechanical ventilation; (v) use of prone position; (vi) performance of a chest CT scan within the 72 hours prior the first PP. Exclusion criteria were: (i) missing clinical data regarding blood gas analysis performed during the first prone position cycle. Intubated subjects with COVID-19 related ARDS were maintained sedated and paralyzed. Subjects were ventilated using a lung protective ventilatory strategy: low tidal volume (TV 6-8 ml/Predicted Body Weight), medium-high levels (8-12 cmH_2O) of PEEP, respiratory rate between 15-25 breaths per minute, maintaining a plateau pressure below 28 cmH_2O and a driving pressure below 12 cmH_2O, with a target SpO_2 of 92-95%. A PaO_2/FiO_2 ratio below 100 was used as a criterion for prone position.[20]

Clinical management, including the decision to use PP and perform a chest CT scan, was at the discretion of the attending physicians. The final date of follow-up for subject outcomes was July 14th, 2022. For study purposes linked to the regional research network[21], an extensive set of information was prospectively recorded from the day of ICU admission on an electronic report form (REDCap electronic data capture tools). This information included anthropometric and clinical data, severity scores, vital signs, laboratory tests, radiological information, ICU and hospital length of stay (LOS), ICU and hospital survival.

To assess the physiologic effects of pronation, subjects' ventilatory settings were prospectively recorded at three different time points: (i) within two hours before the pronation (Baseline); (ii) during the last four hours of the pronation cycle (Prone); (iii) within 2 to 5 hours after turning the subjects back to the supine position (Supine). At each time point, end-inspiratory and end-expiratory airway occlusion maneuvers were performed to calculate driving pressure and respiratory system compliance[22]. At the same time points, arterial blood gases were drawn to calculate the PaO_2/FiO_2 ratio and the ventilatory ratio (VR)[22,23].

Definitions

Subjects were defined as "oxygen responders" (Oxy-R) to PP according to two different definitions previously applied in the literature: i) the PaO_2/FiO_2 ratio increased by$\geq$ 20 mmHg during prone ventilation as compared to baseline values in supine position[1]. Similarly, "oxygen non-responder" (Oxy-NR) were defined as those subjects in whom this condition was not satisfied. ii) The median PaO_2/FiO_2 ratio increase observed during prone ventilation was used as cut-off, defining Oxy-R subjects with a PaO_2/FiO_2 ratio above the median value and Oxy-NR when below[24]. The change in the ventilatory ratio was used to define the response in terms of CO_2 clearance. Subjects were defined as CO_2-responder (CO_2R) when the VR decreased during pronation as compared to supine, while CO_2-non-responder (CO_2NR) when the VR increased or did not change.

CT scan acquisition and image analysis

All CT images were acquired on 4 scanners of a single vendor (Siemens AG, Forchheim, Germany) and with the same acquisition protocol for chest examinations, employing an automatic exposure control (AEC) and an automatic selection of the tube voltage and "sharp" reconstruction algorithm.

All CT series were exported from the Picture Archive Communication System (PACS) to a dedicated workstation for automatic image analysis. A dedicated processing software developed in Python language was used, as previously described [25–27]. Briefly, (i) the pipeline rescales CT images to a slice thickness of 3 mm; (ii) performs, for each slice, automatic segmentation of the left and right lungs; and (iii) calculates the relative distribution of Hounsfield Units (HU) of the segmented regions of interest.

In this work, the following metrics were considered: volume (V_{lung} [ml]), Hounsfield Unit related to the lung density (ρ [HU]) and mass (m [g]). The volume and the density were calculated, respectively, as the number of voxels multiplied by the physical voxel dimension and their average HU value of the selected region of interest. The mass was calculated using the following formula:

$$Lung\ tissue\ mass = \rho \cdot V_{lung} * (1000 - HU)/1000$$

For each CT image, all these metrics were calculated for both lungs, obtained as the sum of the segmentations of the right and left lungs, and in 4 different density regions according to classical aeration thresholds [12]: hyperinflated lung [-1000:-900] HU, well-aerated lung [-900:-500] HU, poorly aerated lung [-500:-100] HU and non-aerated lung [-100:+100] HU[28].

Furthermore, a geometric subdivision of the entire (both lungs) region of interest was performed. The masks were divided into ten different regions equally spaced along the sterno-vertebral axis and for each sub-region, the previous metrics were calculated.

Statistical analysis

No sample size calculation was performed *a priori*, and the sample size is equal to the number of subjects treated in our hospital during the study period. Comparison between continuous variables was performed via Student's t-test using Welsh's correction for unequal variance, Mann-Whitney Rank Sum Test, ANOVA, or Kruskal Wallis test, as appropriate. Differences between categorical variables were assessed using the Chi-Square or Fisher exact test. The continuous relationship between quantitative variables was investigated using linear regression. Data was expressed as mean ± standard deviation or median and interquartile range. Statistical significance was defined as $p < .050$. Analyses were performed with Stata statistical software (Stata, Statistical Software: Release 16. StataCorp LLC, College Station, TX), and graphs were drawn using SigmaPlot v.12.0 (Systat Software, San Jose, CA). The STROBE checklist for observational studies was used.

Results

During the study period, 466 COVID-19 subjects were admitted to the ICU (**Figure 1**). One hundred twenty-five subjects, with a median SAPS II score at ICU admission of 38 [33, 43] were enrolled in the study. Baseline demographic characteristics are summarized in **Table 1**.

Oxygen response to pronation and quantitative CT scan parameters

According to the PaO_2/FiO_2 ratio increased by≥ 20 mmHg definition, 116 subjects (93%) were Oxy-R, while 9 (7%) were Oxy-NR. Oxy-R had a higher BMI (p =.009) and prevalence of hypertension (p = .001) compared to Oxy-NR. The use of non-invasive respiratory support prior to intubation (72% *vs*. 100%, p = .063), its duration (1 [0, 3] vs. 1 [1, 4] days, p = .08), and the use of awake PP prior to intubation (37% vs. 44% p =.44) were similar between Oxy-R and Oxy-NR. No difference in ARDS severity, ventilatory settings, and blood gas parameters were recorded (**Table 2**).

Oxy-R were characterized by higher baseline compliance of the respiratory system (42 ± 11 *vs.* 32 ± 5 ml/cmH_2O, p =<.001). The length of the first pronation performed in the ICU was similar in Oxy-R and Oxy-NR (21 [18, 24] *vs.* 24 [22, 32] hours, p = .08).

During the first PP, Oxy-R improved, as per the definition, the PaO_2/FiO_2 ratio. Moreover, arterial pH and respiratory system compliance increased, while the VR did not change significantly. On the contrary, the PaO_2/FiO_2 ratio did not change in Oxy-NR, while $PaCO_2$ increased in prone position from 48 ± 10 to 59 ± 15 mmHg (p= .011). Consequently, the VR and pH worsened significantly in prone position in this subgroup of subjects (**Figure 2**).

Clinical outcomes divided by Oxy-R and Oxy-NR are summarized in **Table 3**. During the ICU stay, subjects received 4 [2, 6] cycles of pronation for a total amount of 80 [46, 146] hours spent in PP. No differences in ICU length of stay (p = .94) and survival (p = .52) were found between the two groups.

The bilateral qCT scan analysis did not reveal any difference both in mass and density of hyperinflated, well-aerated, poorly aerated, and non-aerated lung tissue when the subjects were divided into Oxy-R and Oxy-NR (**Table 4**).

Lastly, the analysis performed on 10 ventral-dorsal lung segments also did not identify any difference between the two groups (**Figure 3**). For example, the amount of hyperinflated tissue of the ventral region (3.2 ± 2.9 vs. 3.6 ± 2.3 g, p= .66) and non-aerated tissue of dorsal regions (254 ± 161 vs. 263 ± 144 g, p= .85) were similar between Oxy-R and Oxy-NR.

Similar findings were observed when subjects were divided according to the median increase in PaO_2/FiO_2 ratio (87 mmHg). Results can be found in **Tables S1**, **S2**, **S3,** and **S4** of the Online Supplementary Material.

Carbon dioxide response to pronation

Fifty-one (41%) out of 125 subjects improved their ventilatory ratio during PP and were thus defined as CO_2-R, while the remaining 74 subjects were defined as CO_2-NR. Baseline demographic characteristics are summarized in **Table S5**. Before PP, CO_2-R were characterized by higher tidal volume (6.9 ± 1.0 vs. 6.6 ± 0.8 ml/kg, p =.019), respiratory rate (21 ± 4 vs. 18 ± 3, breath/minute, p<.001), and ventilatory ratio (1.9 ± 0.5 vs. 1.5 ± 0.4, p<.001), to maintain a similar arterial PCO_2 (49 ± 9 vs. 46 ± 9 mmHg, p = .09) as compared to CO_2 -NR (**Table S6**). No differences in days of ventilation (p = .94), ICU length of stay (p = .43), or ICU mortality (p =

.46) were found between the two groups (**Table S7**). Similarly, no differences in qCT results were found between CO_2-R and CO_2-NR (**Table 5**).

Discussion

The use of chest CT scans has permanently changed our understanding of ARDS through its morphological assessment and quantitative analysis of density distribution[12]. For these reasons, this radiological examination is extensively used in some centers to evaluate lung structure, disease extension, response to lung recruitment[15], and evolution of disease. In the context of the outbreak of a novel infectious disease leading to pneumonia and respiratory failure, these concepts were broadly applied. This allowed us to study retrospectively a large number of CT scans of critically ill, mechanically ventilated subjects with COVID-19 related ARDS undergoing PP. Our aim was to evaluate whether the different responses in terms of gas exchange during the first PP were associated with different baseline qCT scan characteristics. In the 125 subjects studied, 93% improved their oxygenation during the first PP, and 41% improved their ventilatory ratio. No relationship was found between qCT scan parameters and both oxygen and CO_2 response to PP. Similar results were observed when dividing the population according to the median increase in PaO_2/FiO_2 ratio.

Moreover, we confirmed that the Oxy-R were characterized by higher baseline compliance and lower driving pressure as compared to the Oxy-NR. Of note, the time spent in PP did not differ between the two groups.

During the COVID-19 pandemic, pronation was broadly used in mechanically ventilated patients[1,29–31]. In line with previous data[1], most of the studied subjects improved their oxygenation during the first PP. In his work, Aalinezhad and colleagues identified in COVID-19 subjects a relationship between the severity of lung involvement measured at CT scan and blood oxygenation[32]. Moreover, the possibility of predicting lung recruitment from a single static baseline CT scan using a machine-learning approach has recently been described[33]. In classic

ARDS, lung perfusion is similar in prone and supine position, being slightly unbalanced towards dorsal lung regions[34,35]. According to this characteristic, the improvement in PaO_2/FiO_2 ratio in PP should parallel the variation in density distribution, corresponding to an increase in well-aerated lung tissue in the dorsal areas of the lungs. Despite these premises, in classic ARDS, Papazian and colleagues found no correlation between baseline qCT data and PaO_2/FiO_2 ratio response to pronation[36]. In addition, similarly to what has been observed in non-intubated COVID-19 subjects[18], we were not able to identify a correlation between baseline qCT-scan characteristics and PaO_2/FiO_2 ratio response during PP.

The negative findings of these studies might have several explanations. Quantitative CT data accurately describe lung parenchymal density, while they do not assess pulmonary perfusion. This aspect might be of utmost importance in COVID-19 associated ARDS subjects. Indeed, this disease is characterized by (i) impairment of hypoxic vasoconstriction leading to a marked ventilation/perfusion mismatch[37–39], and (ii) the diffuse presence of pulmonary microthrombosis[40]. Since both these vascular defects can be diffused to all the lungs, irrespective of gravitational distribution (dependent *vs.* non-dependent), and regardless of the parenchymal aspect assessed with CT scan, a dissociation between aeration/ventilation and gas exchange has been described in COVID-19 associated ARDS subjects [38]. It is thus conceivable that, in addition to the unknown potential for lung recruitment, the variable and unpredictable lung perfusion changes further hinder the prediction of the response solely based on baseline qCT information. In addition, the different potential involvement of pulmonary vasculature could justify the broad spectrum of oxygen response to pronation reported in the different studies, going from 35% up to 93% [1,2,18,24,41,42]. Interestingly, and in line with this reasoning, in our population, no difference in qCT characteristics was observed between moderate and severe COVID-19 associated ARDS subjects **(Table S8)**.

A second possible explanation of the different responses to pronation might be the disease time course. Indeed, despite the lack of statistical significance, the time between symptoms onset and first pronation was longer in Oxy-NR, possibly resulting in a more severe disease stage, as suggested by the lower respiratory system compliance. In line with this hypothesis, a decreasing response to PP (in terms of oxygenation) has been described as a consequence of lung consolidation toward organizing fibrotic pneumonia[13,43,44]. Regardless of this potential explanation, no relevant differences in gas exchange, lung weight or non-aerated lung tissue were noted between Oxy-R and Oxy-NR.

Response to pronation

In response to PP, Oxy-R increased slightly, but significantly their respiratory system compliance, which remained higher than baseline after re-supination. The improvement of the PaO_2/FiO_2 ratio paralleled respiratory compliance, except for a slight decrease after re-supination. Notably, these variations were not mirrored by the VR, which did not change significantly.

Fossali *et al.* performed a physiological study exploring the early changes after pronation in COVID-19 associated ARDS subjects performing CT scans both in supine and prone positions[45]. They demonstrated that PP significantly decreased the weight of non-aerated and hyperinflated lung tissue and increased the amount of normally aerated lung. Moreover, the regional response to PP was not homogenous, as demonstrated by the remarkable recruitment in the dorsal regions and derecruitment in the ventral. However, in our population, Oxy-R and Oxy-NR, despite having similar baseline amounts of hyperinflated ventral tissue and non-aerated dorsal tissue, demonstrated markedly different responses in terms of lung mechanics and gas exchanges during PP. Notably, also in Fossali's work [45], no association between the amount of ventral derecruitment or dorsal recruitment and the oxygen response was found. Taken together, our results and the findings of this author foster two considerations: *first*, in COVID-19 subjects, the oxygen response to pronation is most likely not predictable from a static baseline CT scan; *second*, the observed increase in oxygenation is possibly due mainly to the improvement of the ventilation/perfusion matching related to a persistency of perfusion in the vertebral part of the thorax and a reopening of the dorsal collapsed lung [46–49]. This second hypothesis is corroborated by the study of Richter *et al.*[47], who demonstrated that the oxygenation response to pronation in ARDS patients was consequent to an improvement in ventilation /perfusion match due to the unchanged perfusion in the dorsal part of the thorax associated with a reopening of the dorsal collapsed lung. This mechanism, also described using the ventilation/perfusion tools of electrical impedance tomography in classical ARDS subjects[50], was confirmed in COVID-19-associated ARDS[51,52].

In Oxy-NR, no variations in respiratory compliance or PaO_2/FiO_2 ratio were observed. Furthermore, differently from Oxy-R, they experienced an increase in VR and $PaCO_2$ that persisted after the re-supination. This observation points toward an increased dead space. As an increase in hyperinflation is unlikely the underlying mechanism, we think that also in this case, the worsening of ventilation/perfusion might be the cause.

Of note, also when dividing the population according to their response in terms of CO_2 clearance (*i.e.*, variation in VR) no difference in baseline qCT data was observed.

Automated CT scan segmentation

Despite the absence of association between CT scan characteristics and response to PP, CT exams represent the gold standard for evaluating the alterations of lung parenchyma, even in the early stages of the disease, when the subject has few or no symptoms. Moreover, it is also a useful tool for monitoring the disease along its course[11,53].

In addition to the classical qualitative visual image interpretation, the automated and integrated workflow of image analysis allows to extract several objective metadata quantitative information retained in the image, such as parenchymal density and volume, and permits the definition of lung compartments based on the different degrees of aeration [12]. Although quantitative CT image analysis could be extremely informative, some aspects need to be considered for its use in clinical practice. In this work, an algorithm for automatic segmentation of lungs in CT images has been employed[25], which drastically reduces analysis time and enables real-time quantitative results through the use of dedicated in-house software. Avoiding the time-consuming task of drawing the lung boundaries (selection of regions of interest), the physician can thus focus more on interpreting the results of the obtained quantitative metrics.

Limitations

Several limitations have to be addressed for this study. *First*, due to the retrospective nature of the study and the low numerosity of Oxy-NR, our analyses could be underpowered to identify any difference in qCT characteristics; a controlled methodology and more homogeneous groups may produce different results. *Second*, the CT scans were performed for clinical purposes and retrospectively used for the analyses. Thus, no standardization of ventilation mode, nor respiratory phase (*e.g.*, inspiratory pause) was performed during CT scan acquisition. *Third*, no data regarding perfusion of the lung was available. Consequently, the pathophysiological role of ventilation/perfusion matching in explaining oxygen and CO_2 responses to pronation can only be hypothesized. *Finally*, the trunk inclination angle used during the respiratory mechanics measurement was not standardized [54–56].

Conclusion

In conclusion, most COVID-19 related ARDS subjects improve their oxygenation at the first pronation cycle. Our study performed on a large population of critically ill, mechanically ventilated subjects with COVID-19 related ARDS suggests that quantitative data obtained from a baseline CT scan are neither associated with the oxygen response, nor with the response in terms of carbon dioxide elimination.

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Figure legends

Figure 1. Study flow chart. *Acronyms: ARDS: acute respiratory distress syndrome; CT: computed tomography; PP: prone position.*

Figure 2. Variation of clinical parameters during the first pronation cycle of oxygen responders (red circle) and oxygen non-responders (black square) to pronation. Oxygen Responders were defined as the subjects whose PaO_2/FiO_2 ratio increased by≥ 20 mmHg during prone ventilation as compared to baseline values in supine position. Panel A represented the variations of respiratory system compliance. Panel B represented the ratio variations between arterial partial pressure of oxygen and inspiratory fraction of oxygen. Panel C represents the variations in pH. Panel D represented the variations in respiratory ratio.

Figure 3. Ventral-dorsal (1 to 10 segment) regional lung tissue distribution subjects divided by oxygen responders (black bars) and oxygen non-responders (grey bars) to pronation. Oxygen Responders were defined as the subjects whose PaO_2/FiO_2 ratio increased by≥ 20 mmHg during prone ventilation as compared to baseline values in supine position.

Quick Look

Current Knowledge

Chest Computed Tomography (CT) was broadly used in COVID-19 pandemic to facilitate diagnosis and quantify the degree of disease extension. Recently, a relationship between the dorsal non-aerated tissue quantified at the CT scan and the gas exchange response to prone position was demonstrated in classical ARDS, but clinical studies have not confirmed these findings in COVID-19 related ARDS.

What This Paper Contributes To Our Knowledge

No relationship between dorsal non-aerated tissue quantified at the CT scan analysis, and both oxygen and carbon dioxide response to pronation was found. Quantitative CT scan imaging should not be accounted for when deciding whether to use prone position in intubated COVID-19 related ARDS subjects.

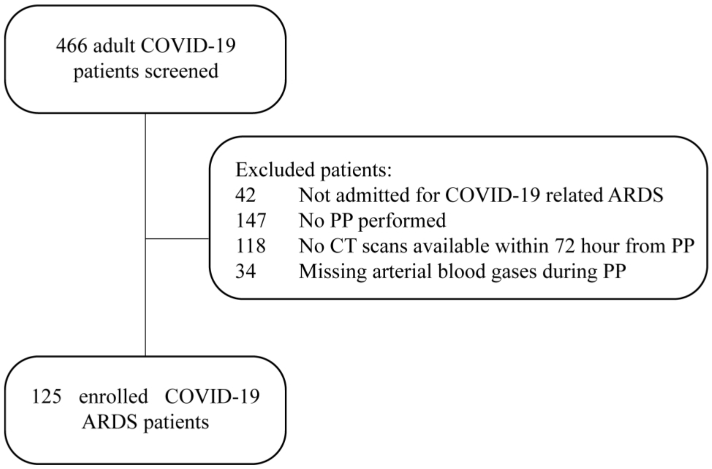

Figure 1. Study flow chart. Acronyms: ARDS: acute respiratory distress syndrome; CT: computed tomography; PP: prone position.

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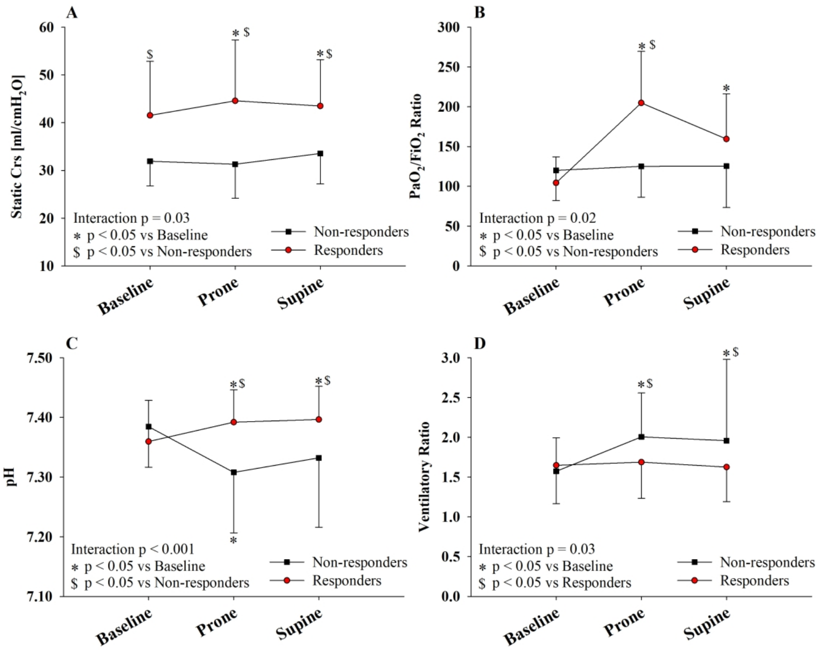

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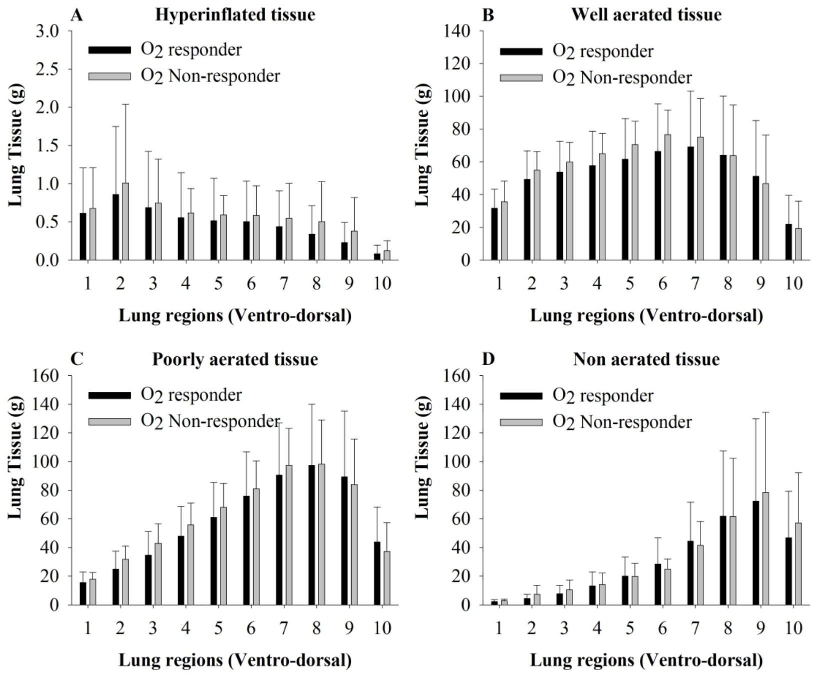

Figure 3. Ventral-dorsal (1 to 10 segment) regional lung tissue distribution subjects divided by oxygen responders (black bars) and oxygen non-responders (grey bars) to pronation. Oxygen Responders were defined as the subjects whose PaO2/FiO2 ratio increased by≥ 20 mmHg during prone ventilation as compared to baseline values in supine position.

253x203mm (300 x 300 DPI)

Table 1. Population demographic characteristics at ICU admission divided by oxygen response to pronation

Variables	Total (N = 125)	Oxygen Non-responders (N = 9)	Oxygen Responders (N = 116)	p-value
Sex, Female n (%)	30 (24)	3 (33)	27 (23)	.45
Age, years	62 ± 11	67 ± 8	61 ± 11	.08
Weight, kg	86 ± 19	74 ± 9	87 ± 19	.001
Height, cm	171 ± 9	169 ± 7	171 ± 9	.58
BMI, kg/m^2	30 ± 6	26 ± 4	30 ± 6	.009
Comorbidities:				
Hypertension, n (%)	64 (51)	0 (0)	64 (55)	.001
Diabetes, n (%)	22 (18)	1 (11)	21 (18)	.51
Active Smoke, n (%)	5 (4)	0 (0)	5 (4)	.68
Obesity, n (%)	38 (30)	1 (11)	37 (32)	.18
Cancer, n (%)	14 (11)	3 (33)	11 (9)	.063
CKD, n (%)	9 (7)	0 (0)	9 (8)	.50
COPD, n (%)	13 (10)	0 (0)	13 (11)	.36
Atrial Fibrillation, n (%)	8 (6)	0 (0)	8 (7)	.54
CAD, n (%)	15 (12)	1 (11)	14 (12)	.71
Liver disease, n (%)	10 (8)	0 (0)	10 (9)	.46
SOFA	5 [4, 6]	4 [2, 6]	5 [4, 6.5]	.23
SAPS II	38 [33, 43]	41 [35, 43]	38 [33, 43.5]	.63
Days between the onset of symptoms and CT scan, days	10±6	14±7	10±6	.13
Days between the onset of symptoms and first pronation, days	11±6	15±6	10±6	.073

Subjects were defined as "oxygen responders" (Oxy-R) to PP if the PaO_2/FiO_2 ratio increased by≥ 20 mmHg during prone ventilation as compared to baseline values in supine position.

Similarly, "oxygen non-responder" (Oxy-NR) were defined as those subjects in whom this condition was not satisfied. *Acronyms: BMI body mass index; CAD coronary arterial disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CT computed tomography; ICU: intensive care unit; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment.*

Table 2. Ventilatory parameters of the population divided by oxygen response to pronation in supine position before the first pronation

Variables	Total (N = 125)	Oxygen Non-responders (N = 9)	Oxygen Responders (N = 116)	p-value
ARDS Severity				.53
Mild n (%)	1 (0.8)	0 (0.0)	1 (1)	
Moderate n (%)	65 (52.0)	6 (67)	59 (51)	
Severe n (%)	59 (47.2)	3 (33)	56 (48)	
Ventilator setting:				
Tidal Volume/PBW, ml/kg	6.7 ± 0.9	6.6 ± 1.0	6.8 ± 0.8	.13
RR, breath/minute	19 ± 3	20 ± 4	19 ± 3	.86
PEEP, cm H_2O	12 ± 2	12 ± 2	12 ± 2	.29
Plateau Pressure, cm H_2O	24 ± 3	24 ± 3	23 ± 3	.42
Crs, ml/cm H_2O	41± 11	32 ± 5	42 ± 11	<.001
Driving Pressure, cm H_2O	11 ± 3	13 ± 2	11 ± 3	.08
Arterial blood Gas:				
pH	7.36 ± 0.07	7.38 ± 0.07	7.36 ± 0.07	.32
$PaCO_2$, mm Hg	47 ± 9	48 ± 10	47 ± 9	.78
Ventilatory Ratio	1.6 ± 0.5	1.6 ± 0.4	1.6 ± 0.5	.62
PaO_2, mm Hg	77 ± 16	80 ± 10	77 ± 16	.44
FiO_2, %	0.8 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	.36
PaO_2/FiO_2	103 [82, 123]	113 [89, 142]	102 [81, 122]	.22

Subjects were defined as "oxygen responders" (Oxy-R) to PP if the PaO_2/FiO_2 ratio increased by≥ 20 mmHg during prone ventilation as compared to baseline values in supine position. Similarly, "oxygen non-responder" (Oxy-NR) were defined as those subjects in whom this condition was not satisfied. *Acronyms: ARDS: acute respiratory distress syndrome; Crs:*

compliance of the respiratory system; FiO_2 inspiratory fraction of oxygen; $PaCO_2$ arterial partial pressure of carbon dioxide; PaO_2 arterial partial pressure of oxygen; PBW: predicted body weight, PEEP: positive end-expiratory pressure; RR: respiratory rate.

Table 3. Clinical outcomes of the population divided by oxygen response to pronation

Variables	Total (N = 125)	Oxygen Non-responders (N = 9)	Oxygen Responders (N = 116)	p-value
Number of Pronation, n	4 [2, 6]	3 [2, 5]	4 [2, 7]	.27
Total Pronation Time, hour	80 [46, 146]	92 [47, 139]	79 [44, 148]	.82
iNO, n (%)	32 (26)	3 (33)	29 (25)	.69
Days of Ventilation	30 [17, 41.5]	42 [19, 57]	29 [17, 39]	.25
Tracheostomy, n (%)	76 (61)	5 (56)	71 (61)	.74
Hospital LOS, days	45 [26, 65]	57 [22, 62]	44 [26, 65]	.94
ICU LOS days	33 [19, 45]	43 [10, 50]	33 [20, 45]	.94
ICU Outcome				.52
Deceased n (%)	51 (41)	4 (44)	47 (40)	
Discharged n (%)	74 (59)	5 (56)	70 (60)	

Subjects were defined as “oxygen responders” (Oxy-R) to PP if the PaO_2/FiO_2 ratio increased by≥ 20 mmHg during prone ventilation as compared to baseline values in supine position. Similarly, “oxygen non-responder” (Oxy-NR) were defined as those subjects in whom this condition was not satisfied. *Acronyms: ICU: intensive care unit; iNO: inhaled nitric oxide; LOS: length of stay.*

Table 4. Baseline quantitative CT parameters of the population divided for the oxygen response to pronation.

Variables	All patients (N = 125)	Oxygen Non-responders (N = 9)	Oxygen Responders (N = 116)	p-value
Bilateral Lung				
Volume, ml	3526 ±1009	3816 ±757	3503 ±1025	.27
Density, HU	-545 ±106	-562 ±58	-544 ±109	.42
Tissue mass, g	1541 ±390	1654 ±304	1532 ±396	.28
Hyper inflated lung				
Volume, ml	160 ±157	189 ±126	158 ±159	.50
Density, HU	-968 ±2	-968 ±2	-968 ±2	.72
Tissue mass, g	5 ±5	6 ±3	5 ±5	.46
Well aerated lung				
Volume, ml	2092 ±895	2283 ±532	2077 ±917	.31
Density, HU	-740 ±31	-752 ±17	-739 ±32	.066
Tissue mass, g	530 ±208	568 ±13	527 ±213	.43
Poorly aerated lung				
Volume, ml	891 ±324	939 ±242	887 ±330	.56
Density, HU	-343 ±20	-345 ±16	-343 ±20	.75
Tissue mass, g	584 ±210	615 ±158	582 ±214	.57
Non aerated lung				
Volume, ml	319 ±192	335 ±157	317 ±195	.75
Density, HU	-51 ±8	-50 ±6	-51 ±8	.75
Tissue mass, g	303 ±185	319 ±150	302 ±188	.76

Subjects were defined as "oxygen responders" (Oxy-R) to PP if the PaO_2/FiO_2 ratio increased by≥ 20 mmHg during prone ventilation as compared to baseline values in supine position.

Similarly, “oxygen non-responder” (Oxy-NR) were defined as those subjects in whom this condition was not satisfied. *Acronyms: CT: computed tomography.*

Table 5. Baseline quantitative CT parameters of the population divided for the carbon dioxide response to pronation.

Variables	Total (N = 125)	CO_2 Non-responders (N = 74)	CO_2 Responders (N = 51)	p-value
Bilateral Lung				
Volume, ml	3526 ±1009	3502 ±1030	3560 ±987	.75
Density, HU	-545 ±106	-546 ±94	-545 ±123	.99
Tissue mass, g	1541 ±390	1534 ±377	1551 ±412	.89
Hyper inflated lung				
Volume, ml	160 ±157	144 ±136	184 ±182	.37
Density, HU	-968 ±2	-968 ±2	-968 ±2	.58
Tissue mass, g	5 ±5	4 ±4	6 ±5	.36
Well aerated lung				
Volume, ml	2092 ±895	2087 ±885	2099 ±918	.96
Density, HU	-740 ±31	-735 ±29	-748 ±33	.018
Tissue mass, g	530 ±208	542 ±216	512 ±198	.55
Poorly aerated lung				
Volume, ml	891 ±324	929 ±323	835 ±320	.07
Density, HU	-343 ±20	-346 ±19	-338 ±21	.033
Tissue mass, g	584 ±210	606 ±207	553 ±212	.10
Non aerated lung				
Volume, ml	319 ±192	287 ±157	366 ±228	.13
Density, HU	-51 ±8	-52 ±6	-49 ±9	.19
Tissue mass, g	304 ±185	272 ±150	349 ±220	.12

Acronyms: CT: computed tomography.