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Please cite this article as: Lemmers DHL, Abu Hilal M, Bnà C, *et al*. Pneumomediastinum and subcutaneous emphysema in COVID-19: barotrauma or lung frailty?. *ERJ Open Res* 2020; in press (https://doi.org/10.1183/23120541.00385-2020).

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Pneumomediastinum and subcutaneous emphysema in COVID-19: barotrauma or lung frailty?

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Authors' contributions

Each author has contributed significantly to, and is willing to take public responsibility for, the following aspects of the study:

Design: D.H.L. Lemmers, M. Abu Hilal, C. Bna, G. Natalini

Data Acquisition: D.H.L. Lemmers, M. Abu Hilal, G. Natalini, C. Prezioso, E. Cavallo, N. Nencini, S. Crisci

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Critical Revision: D.H.L. Lemmers, M. Abu Hilal, C. Bna, C. Prezioso, E. Cavallo, N. Nencini, S. Crisci, F. Fusina, G. Natalini

Conflict of interest statement

The authors have no conflicts of interest to declare.

Ethical approval

Our referral Ethics Committee approved a waiver of consent for this retrospective study. Protocol number: NP 4142

Availability of data and material

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

Funding

This research received no specific grant from any funding agency in the public, commercial, or non-for-profits sector.

Abstract

Background.
In mechanically ventilated Acute Respiratory Distress Syndrome (ARDS) patients with novel coronavirus disease (COVID-19), we frequently recognized the development of pneumomediastinum and/or subcutaneous emphysema despite employing a protective mechanical ventilation strategy. The purpose of this study was to determine if the incidence of pneumomediastinum/subcutaneous emphysema in COVID-19 patients was higher than in ARDS patients without COVID-19 and if this difference could be attributed to barotrauma or to lung frailty.
Methods.
We identified the cohort of patients with ARDS and COVID-19 ("CoV-ARDS"), and the cohort of patients with ARDS from other causes ("noCoV-ARDS").
Patients with CoV-ARDS were admitted to ICU during the COVID-19 pandemic and had microbiologically confirmed SARS-CoV-2 infection. NoCoV-ARDS was identified by an ARDS diagnosis in the five years before the COVID-19 pandemic period.
Results.
Pneumomediastinum/subcutaneous emphysema occurred in 23 out of 169 (13.6%) patients with CoV-ARDS and in 3 out of 163 (1.9%) patients with noCoV-ARDS ($p<0.001$). Mortality was 56.5% in CoV-ARDS patients with pneumomediastinum/subcutaneous emphysema and 50% in patients without pneumomediastinum ($p=0.46$).
CoV-ARDS patients had a high incidence of pneumomediastinum/subcutaneous emphysema despite the use of low tidal volume (5.9∓0.8 ml/kg ideal body weight) and low airway pressure (plateau pressure 23∓4 cmH_2O).
Conclusions.
We observed a seven-fold increase in pneumomediastinum/subcutaneous emphysema in CoV-ARDS. An increased lung frailty in CoV-ARDS could explain this finding more than barotrauma, which, according to its etymology, refers to high transpulmonary pressure.

Keywords
Pneumomediastinum, subcutaneous emphysema, COVID-19, ARDS, barotrauma, ventilator-induced lung injury, Intensive Care Unit, mechanical ventilation.

Take home message

Pneumomediastinum was more frequent in COVID-19 patients with ARDS despite the use of a protective ventilatory approach. Lung frailty and not barotrauma appears therefore as the main cause of this finding.

Introduction

Since the beginning of the novel coronavirus disease 2019 (COVID-19) outbreak in Lombardy, Italy, Fondazione Poliambulanza hospital has treated over 2200 affected patients, and more than 160 of them have been admitted to the Intensive Care Unit (ICU) for treatment of Acute Respiratory Distress Syndrome (ARDS) secondary to COVID-19.

All patients admitted to ICU underwent invasive mechanical ventilation with protective criteria aimed at preventing ventilator-induced lung injury (VILI). The current approach to protective ventilation, which became universally accepted after the ARDS Network trial [1], is based on the reduction of tidal volume to about 6 ml/kg of ideal body weight while maintaining the airway plateau pressure below 30 cmH_2O [2]. In the last two decades, as a consequence of this strategy, the occurrence of ~~the~~ main macroscopic signs of barotrauma such as pneumothorax, pneumomediastinum and subcutaneous emphysema has become very rare [3]. Actually,this type of damage had been rarely seen in our ICU patients with ARDS. Nonetheless, during the COVID-19 pandemic there seemed to be a remarkable increase in pneumomediastinum/subcutaneous emphysema occurrence despite the use of the same unchanged protective mechanical ventilation protocol. On the other hand, a decrease in lung compliance, age and underlying lung disease (such as interstitial lung disease, chronic obstructive pulmonary disease, cystic fibrosis, and certain lung infections like Pneumocystis Jirovecii pneumonia) are known risk factors for non-trauma related pneumomediastinum[4]. The causes of the apparent increase in pneumomediastinum and subcutaneous emphysema in our COVID-19 patients were not clear.The purpose of this study was to determine if the incidence pneumomediastinum/subcutaneous emphysema in mechanically ventilated COVID-19 patients admitted to ICU was higher than in ARDS patients without COVID-19, and if this could be attributed to barotrauma or rather to lung frailty.

Material and Methods

Study design and participants

The referral Ethics Committee approved a waiver of consent from individual patients due to the retrospective nature of the study. Inclusion criteria were: (1) age older than 18 years, (2) ARDS diagnosis at ICU admission [5] and (3) invasive mechanical ventilation.

Two cohorts were created: 1) patients with ARDS [5] and COVID-19 ("CoV-ARDS"), who were admitted to ICU from the beginning of the COVID-19 pandemic period in Italy. We considered the pandemic period as starting on February 18th 2020, which was the day of the first diagnosis of SARS-CoV-2 infection in an Italian patient. SARS-CoV-2 infection was diagnosed with a positive real time reverse transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2 on biological samples. Patients admitted until April 15th 2020 were included in the study. 2) patients admitted from January 2015 to December 2019 to ICU with an ARDS diagnosis [5], before the beginning of the COVID-19 pandemic period in Italy ("noCoV-ARDS").
All data and variables were extracted from the electronic patient registry. The diagnosis of pneumomediastinum/subcutaneous emphysema was confirmed by CT-scan or chest X-ray.

Outcome measures and explanatory variables

The outcome variable was the incidence of pneumomediastinum/subcutaneous emphysema in patients with ARDS secondary to COVID-19. Response variables were patient related characteristics such as age, gender, body mass index and comorbidities, and characteristics related to acute respiratory failure and mechanical ventilation, such as positive end-expiratory pressure (cmH_2O), peak airway pressure (cmH_2O), plateau airway pressure (cmH_2O), pH, $PaCO_2$ (mmHg), PaO_2/FIO_2 (mmHg), compliance of the respiratory system (ml/cmH_2O), minute ventilation (l/min), corrected minute ventilation (l/min), and tidal volume/ideal body weight (ml/kg). Corrected minute ventilation, an indirect estimation of dead space, was calculated as minute ventilation$\bullet PaCO_2/40$. [5].

Statistical analysis

Variables were presented with frequencies and percentages for categorical variables, as median (1st-3rd quartile) for non-normal distributed continuous variables and as mean$\mp$standard deviation for normal distributed continuous variables. The difference in explanatory variables was assessed using a Chi-square test or Fisher test for dichotomous and categorical variables, a t-test for normally distributed continuous variables, and a Mann-Whitney U test for non-normal distributed continuous variables. A p value lower than 0.05 was considered significant. Statistical analyses were performed with R 3.6.3 (R Core Team, 2020. R Foundation for Statistical Computing).

Results

Baseline characteristics

One hundred and sixty nine CoV-ARDS patients and 163 noCoV-ARDS patients were included in the study. Patients' characteristics are shown in Table 1.

Patients with CoV-ARDS were younger, more frequently male, with an higher body mass index and a lower prevalence of diabetes mellitus and chronic obstructive pulmonary disease than noCoV-ARDS patients. Pneumomediastinum/subcutaneous emphysema incidence and in-hospital mortality were higher in CoV-ARDS than in noCoV-ARDS. CoV-ARDs patients were ventilated with a higher PEEP and lower tidal volume/ideal body weight than noCoV-ARDS. Compliance of the respiratory system and PaO_2/FIO_2 were lower in CoV-ARDS patients, whereas corrected minute ventilation was higher when compared to noCoV-ARDS. $PaCO_2$ was higher in CoV-ARDS than in noCoV-ARDS, as a result of similar minute ventilation in presence of increased dead space estimation.

Pneumomediastinum/subcutaneous emphysema

Twenty-three of the 169 patients admitted to ICU with CoV-ARDS developed pneumomediastinum/subcutaneous emphysema. The characteristics of patients with and without pneumomediastinum/subcutaneous emphysema in CoV-ARDS on the day of ICU admission are shown in Table 2. The only significant difference between patients with and without pneumomediastinum/subcutaneous emphysema was a lower minute ventilation on the day of ICU admission in patients with pneumomediastinum/subcutaneous emphysema. No difference in PEEP, plateau pressure, tidal volume/ideal body weight and compliance were observed.

Table 3 compares mechanical ventilation and gas exchange data on the day of ICU admission and on the day of pneumomediastinum/subcutaneous emphysema occurrence for the 23 CoV-ARDS patients who developed pneumomediastinum. PEEP and plateau pressure were lower on the day on which pneumomediastinum/subcutaneous emphysema developed than on the day of ICU admission, and tidal volume was slightly increased. The average day of appearance of pneumomediastinum/subcutaneous emphysema for CoV-ARDS patients was 3.5 (0.25-7.75) days.

Discussion

To the best of our knowledge, this study represents to date the largest cohort of patients who developed pneumomediastinum/subcutaneous emphysema. The occurrence of pneumomediastinum/subcutaneous emphysema was rare in noCOV-ARDS, while it was more frequent in CoV-ARDS even if the same protective ventilatory approach was applied.

The causes of pneumomediastinum in mechanically ventilated patients can be multifactorial [4]. Pulmonary barotrauma in patients with ARDS has traditionally been related to the development of high airway pressure associated with high tidal volume ventilation (approximately 12 ml/kg ideal body weight) [6–8]. Despite the fact that airway pressure in CoV-ARDS patients was higher than in noCoV-ARDS, the criteria of protective ventilation were respected in CoV-ARDS patients as well. Indeed, in CoV-ARDS patients' average plateau pressure was 23 cmH_2O a value lower than the threshold of 30 cmH_2O recommended by current guidelines [2] and lower than the average 26 cmH_2O recorded at the onset of severe ARDS in the LUNG SAFE study patients [2,9]. Moreover, tidal volume was lower (5.9 ml/kg ideal body weight on average) than what has been previously found (7.5 ml/kg ideal body weight on average in the LUNG SAFE [9]) and in line with guidelines recommendations [2]. In the CoV-ARDS cohort, patients who developed pneumomediastinum/subcutaneous emphysema had similar airway pressure on the day of ICU admission to patients who did not develop it. Moreover airway pressures were lower on the day pneumomediastinum/subcutaneous emphysema were noticed than on the day on which mechanical ventilation was started.

Considering this, pneumomediastinum/subcutaneous emphysema in CoV-ARDS do not appear to be associated with the classic barotrauma mechanism which, according to its etymology, refers only to high transpulmonary pressures [10]. This is in agreement with a previously published study on more than 5000 mechanically ventilated patients, in which the presence of air outside the tracheobronchial tree (pneumothorax, pneumomediastinum, subcutaneous emphysema) was unrelated to airway pressures and tidal volume [11]. Therefore, the automatic association between barotrauma and presence of air outside the tracheobronchial tree in mechanically ventilated patients [11,12] should be reconsidered. Actually, the term "barotrauma" should be used in presence of air outside the tracheobronchial tree only when concurrent with elevated airway pressure. In its absence, such condition should not be referred to as barotrauma,

but simply described for what it is (pneumomediastinum, subcutaneous emphysema, pneumothorax). Whenever barotrauma is excluded, the underlying disease should be considered as the cause for the pneumomediastinum/subcutaneous emphysema. In fact, obstructive pulmonary diseases and ARDS are known risk factors for the development of pneumomediastinum/subcutaneous emphysema [11]. All of our patients had ARDS, while chronic obstructive pulmonary disease had a low prevalence and was even less frequent in CoV-ARDS than in noCoV-ARDS patients.

Ground-glass opacities, crazy paving appearance, air space consolidation, bronchovascular thickening and dilatation can be seen on CT scans of COVID-19 patients [13]. In addition, patients with pneumomediastinum can have radiological signs of intraparenchymal lesions such as pneumatocele and interstitial emphysema [14]. Pneumomediastinum/subcutaneous emphysema could be attributed to the Macklin effect as seen in Figure 1. This pathophysiologic process is characterized by alveolar ruptures, air dissection along bronchovascular sheaths, and spreading of the pulmonary interstitial emphysema into the mediastinum. The rupture along the alveolar tree releases alveolar air which centripetally dissects through the pulmonary interstitium along the bronchovascular sheaths toward the pulmonary hila [14,15].

The high incidence of pneumomediastinum/subcutaneous emphysema (13%) observed during the COVID-19 crisis is worrying and deserves a careful assessment. Even though the mortality rate was not significantly different in patients with and without pneumomediastinum/subcutaneous emphysema, future studies should focus on the follow-up of surviving patients who developed pneumomediastinum/subcutaneous emphysema. This is essential in determining its effect on long-term outcomes, such as on lung function or on the development of lung diseases like chronic obstructive pulmonary disease or pulmonary fibrosis [16].

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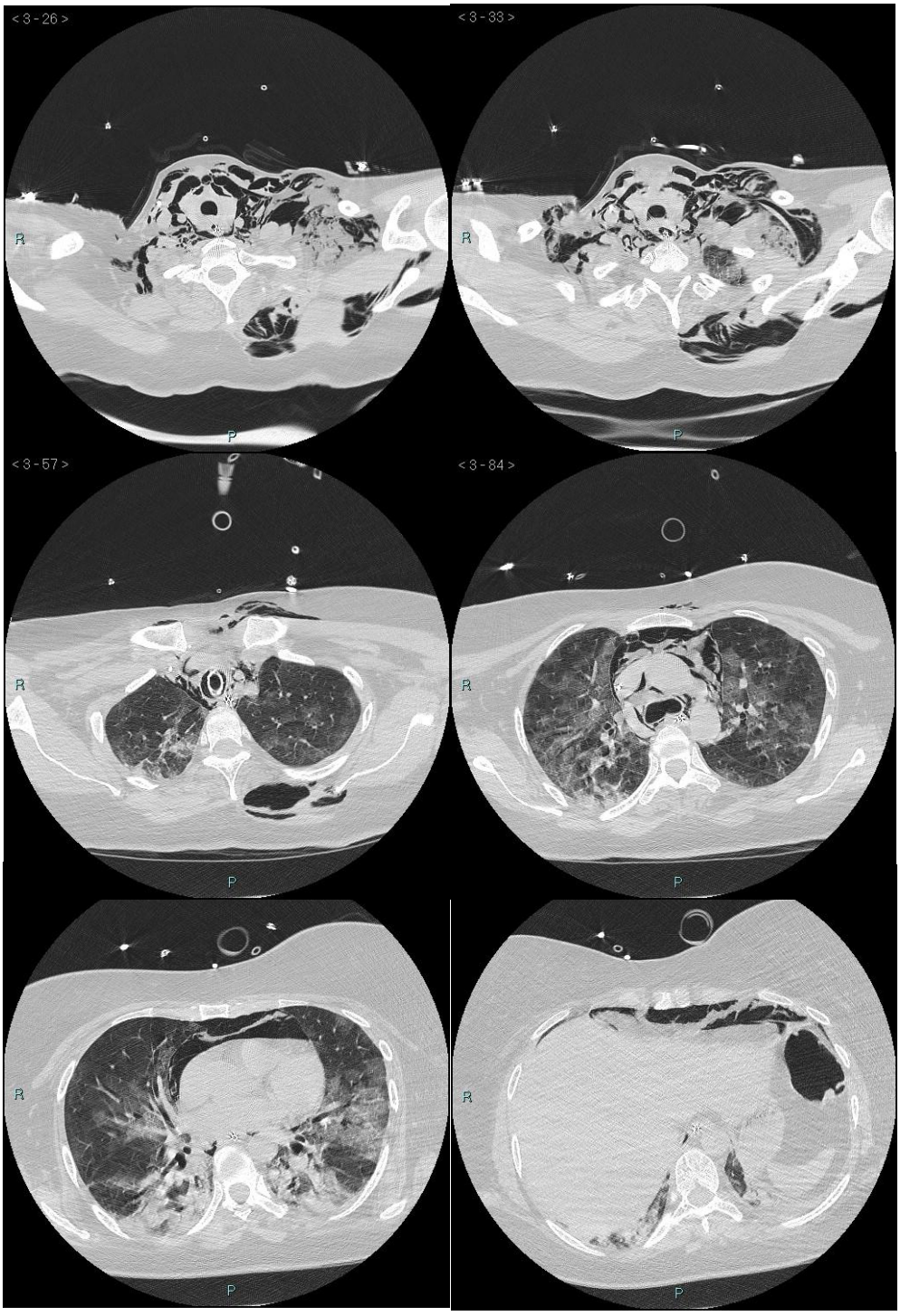
Figure 1



Chest CT-scan, performed in a patient with multiple ground glass lesions and infiltrates (ARDS secondary to COVID-19). The scan shows the Macklin effect due to alveolar rupture, air leakage and dissection along broncho-vascular sheaths with pulmonary interstitial emphysema and pneumomediastinum, that extends widely along the muscle bundles of the chest and neck. A subcutaneous emphysema and extension of pneumomediastinum in the abdomen is also seen.

Table 1. Baseline characteristics on first day of mechanical ventilation and outcomes in patients with ARDS secondary to COVID-19 and ARDS from other diseases

Variables	CoV-ARDS (n=169)	noCoV-ARDS (n=163)	p value
Age (years)	66 (59-71)	72 (62.78)	<0.001
Male sex	133 (78.7%)	106 (65.4%)	0.007
Body mass index (kg/m^2)	28 (25-31)	27 (24-31)	0.02
Diabetes mellitus	26 (15.4%)	47 (29%)	0.003
Arterial hypertension	90 (53.3%)	96 (59.3%)	0.27
Chronic Obstructive Pulmonary Disease	4 (2.4%)	22 (13.5%)	<0.001
Positive end-expiratory pressure (cmH_2O)	12 (10-14)	8 (5-9)	<0.001
Peak airway pressure (cmH_2O)	30∓5	22∓6	<0.001
Plateau airway pressure (cmH_2O)	23∓4	19∓3	<0.001
pH	7·29∓0.12	7·33∓0.14	0.15
$PaCO_2$ (mmHg)	56∓16	46∓12	<0.001
Compliance of the respiratory system (ml/cmH_2O)	28 (22-34)	35 (25-43)	<0.001
Minute ventilation (l/min)	8.8∓1.3	8.7∓2.3	0.62

Corrected minute ventilation (l/min)	12.4 (9.3-15)	9.6 (7.5-11.8)	<0.001
PaO_2/FIO_2 (mmHg)	111 (86-153)	140 (100-198)	<0.001
Tidal volume/ideal body weight (ml/kg)	5.9∓0.8	6.6∓1.3	<0.001
Length of stay in Intensive Care Unit	10 (5-18)	7 (3-20)	0.22
Length of stay in hospital	15 (9-24)	20 (11-33)	0.002
In-hospital mortality	86 (50.9%)	43 (26.6%)	<0.001
Pneumomediastinum/subcutaneous emphysema	23 (13.6%)	3 (1.9%)	<0.001

Data are shown as frequency (%), mean∓standard deviation, median (1^{st}-3^{rd} quartile)

CoV-ARDS: ARDS from COVID-19; noCoV-ARDS: ARDS secondary to other diseases.

Table 2. Baseline characteristics and outcomes in patients with ARDS secondary to COVID-19 with and without pneumomediastinum/subcutaneous emphysema

Variables	With P/SE (n=146)	Without P/SE (n=23)	p value
Age (years)	67 (59-71)	64 (60-70)	0.24
Male sex	118 (80.8%)	15 (65%)	0.09
Body mass index (kg/m^2)	28 (26-31)	27 (25-31)	0.29
Diabetes mellitus	23 (15.8%)	3 (13%)	0.74
Arterial hypertension	79 (54.1%)	11 (47.8%)	0.58
Chronic Obstructive Pulmonary Disease	4 (2.7%)	0 (0%)	1
Positive end-expiratory pressure (cmH_2O)	12 (10-14)	12 (8-15)	0.72
Peak airway pressure (cmH_2O)	29∓5	30∓5	0.56
Plateau airway pressure (cmH_2O)	23∓4	24∓6	0.80
pH, mean SD	7.28∓0.12	7.33∓0.11	0.07
$PaCO_2$ (mmHg)	57∓16	53∓15	0.26
Compliance of the respiratory system (ml/cmH_2O)	27 (22-33)	28 (22-36)	0.55

Minute ventilation (l/min)	8.9∓1.3	8.3∓1.1	0.04
Corrected minute ventilation (l/min)	12.7 (9.4-15)	9.9 (8.4-13.1)	0.07
PaO_2/FIO_2 (mmHg)	114 (86-153)	105 (81-137)	0.21
Tidal volume/ideal body weight (ml/kg)	5.9∓0.8	6.1∓0.9	0.23
Length of stay in Intensive Care Unit	9 (5-18)	11 (6-21)	0.44
Length of stay in hospital	14 (8-23)	18 (12-28)	0.18
In-hospital mortality	73 (50%)	13 (56.5%)	0.46

Data are shown as frequency (%), mean∓standard deviation, median (1^{st}-3^{rd} quartile)

P/SE: pneumomediastinum/subcutaneous emphysema

Table 3. Ventilatory variables of patients with ARDS secondary to COVID-19 who developed pneumomediastinum/subcutaneous (n=23)

Variables	On the first day of mechanical ventilation	On the day of P/SE	p value
Positive end-expiratory pressure (cmH_2O)	12 (8-15)	9 (6-13)	0.002
Peak airway pressure (cmH_2O)	30∓5	29∓5	0.08
Plateau airway pressure (cmH_2O)	24∓5	22∓4	0.045
pH	7.32∓0.09	7.33∓0.13	0.4
$PaCO_2$ (mmHg)	54∓14	53∓12	0.77
Compliance of the respiratory system (ml/cmH_2O)	25 (22-34)	33 (27-40)	0.13
Minute ventilation (l/min)	8.4∓1.2	8.9∓2.1	0.13
Corrected minute ventilation (l/min)	11.5∓4	12.1∓4.1	0.45

PaO_2/FIO_2 (mmHg)	108∓33	131∓76	0.13
Tidal volume/ideal body weight (ml/kg)	6∓0.9	6.7∓1.7	0.008

Data are shown as frequency (%), mean∓standard deviation, median (1^{st}-3^{rd} quartile)

P/SE: pneumomediastinum/subcutaneous emphysema