



Pneumothorax/pneumomediastinum and pre-existing lung pathology in ventilated COVID-19 patients: a cohort study

Gabriella Kecskes^{1^}, Albert Szabo², David Sutori³, Peter Maroti⁴, Gergely Marovics⁴, Tamas F. Molnar^{3,5}

¹Department of Anaesthesiology and Intensive Care, Petz A University Teaching Hospital, Győr, Hungary; ²Department of Radiology, Petz A University Teaching Hospital, Győr, Hungary; ³St. Sebastian Thoracic Surgery Unit, University Teaching Hospital, University of Pécs, Győr, Hungary; ⁴Department of Public Health Medicine, University of Pécs, Pécs, Hungary; ⁵Department of Operational Medicine, Faculty of Medicine, University of Pécs, Pécs, Hungary

Contributions: (I) Conception and design: G Kecskes, TF Molnar; (II) Administrative support: A Szabo, D Sutori; (III) Provision of study materials or patients: G Kecskes; (IV) Collection and assembly of data: G Kecskes; (V) Data analysis and interpretation: G Marovics, P Maroti; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Gabriella Kecskes. Department of Anaesthesiology and Intensive Care, Petz A. University Teaching Hospital, Vasvari P. str. 2-4. 9024., Győr, Hungary. Email: gabriella.kecskes@gmail.com.

Background: There is an increasing number of reports on developing pneumothorax/pneumomediastinum among severe acute respiratory syndrome coronavirus disease 2019 (SARS-COVID-19) patients. The aim of our study was whether pre-existing diffuse lung pathology increases visceral pleural vulnerability resulting in pneumomediastinum and pneumothorax among mechanically ventilated COVID-19 patients?

Methods: A total of 138 consecutive COVID-19 patients admitted to the Intensive Care Unit of Petz Aladár University Teaching Hospital between 1st March 2020 and 1st February 2021 were included. Sixty/138 (43.48%) patients had one or more computer tomography scans of the chest. Analysis was focused on the image defined lung conditions during artificial ventilation.

Results: Thirteen out of 60 ventilated patients developed pneumothorax or pneumomediastinum proven by computer tomography (9.42%). Three/13 patients suffered from pre-existing lung parenchyma pathology, while 10/13 had only COVID-19 infection-related image abnormality. Forty-three/60 patient had healthy lung pre-COVID. Kruskal-Wallis test, Spearman correlation and Cox regression calculations did not reveal any statistically significant result proving increased vulnerability during pressure support therapy and visceral pleural breakdown in patients with pre-existing lung pathologies.

Conclusions: Pre-existing lung pathology does not increase the risk of onset of pneumothorax or pneumomediastinum in comparison with previously healthy lungs of ventilated COVID-19 patients.

Keywords: Pre-existing diffuse lung pathology; barotrauma; pneumothorax (PTX); pneumomediastinum

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Introduction

Pneumothorax (PTX), is an accumulation of free air within the virtual space between visceral and parietal pleura (1). Spontaneous PTX develops in seemingly healthy lung, while secondary PTX needs a lung affected by some underlying

chronic pathology, such as bullous emphysema. The air either enters the pleural space through the chest wall (traumatic PTX) or “inside-out” from the alveoli through the injured visceral pleura into the intrapleural space. Artificial PTX was nearly the exclusive invasive therapy of

[^] ORCID: 0000-0003-1675-9057.



Figure 1 Grade 1 pneumothorax on the left.

tuberculosis for more than half a century (2). The hypothesis list of the possible mechanisms and the predisposing factors for the “spontaneous” free air accumulation is long (3-5). Pneumomediastinum (PM) is a different phenomenon, meaning the presence of extraluminal gas within the mediastinum. The true pathogenesis remains to be obscure in all but the obvious openings/wounds of the tracheobronchial wall and/or oesophagus (6,7).

PTX as a presenting phenomenon was described also in the 2003 severe acute respiratory syndrome (SARS) (8) and there is an increasing number of reports on developing PM/PTX among severe acute respiratory syndrome coronavirus disease 2019 (SARS-COVID-19) patients as well (9-15). The jury is still out on the question regarding the clinical relevance of the PM/PTX, which is reflected in the controversies surrounding the best clinical practice. The question in our non-interventional, observational, prospective, single centre study was whether pre-existing lung pathology increases the chance of developing PTX and PM among mechanically ventilated patients (16). We present the following article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-817/rc>).

Methods

Altogether 138 consecutive patients with polymerase chain reaction confirmed COVID-19 infection were treated at the Intensive Care Unit (ICU) of Petz Aladár University Teaching Hospital, Győr between 1st March 2020 and 1st

February 2021. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Regional Science and Research Ethics Committee of Petz Aladar University Teaching Hospital (No. 76-1-8/2021) and individual consent for this retrospective analysis was waived. Admission criteria to the ICU included $\text{PaO}_2 < 65$ mmHg or O_2 saturation $< 92\%$ on reservoir O_2 bag, or hypotension [mean arterial pressure (MAP) < 70 mmHg] or acidosis, or rapidly deteriorating clinical status due to the impaired gas exchange functions. Based on the currently valid evidence in adult respiratory distress syndrome (ARDS) ventilation strategy, we tried not to exceed the maximum end-inspiratory pressure of 30–35 mbar. Depending on lung compliance, allowing permissive hypercapnia, we set a tidal volume of 6 mL/kg. Basically, we used pressure-controlled ventilation or airway pressure release ventilation (17). Computer tomography (CT) was performed in 60/138 (43.48%) patients. Three independent observers evaluated pre-existing lung pathologies and pleural and mediastinal space abnormalities.

Electronic patient dataset provided checking anamnestic information. All records of the patients included were evaluated with the Hungarian patient-specific (Health Insurance Number coded) electronic database. The analysis was secured by full anonymization protocol. As far as the CT images are concerned, tissue free areas within the pleural space and mediastinal and/or pericardial collection with free air density have been graded. Bullae, pneumokele, fluid-free lung cysts less than 10% of the relevant lobe were categorised as stage I, destroyed lung, covering $> 50\%$ of the ipsilateral hemithorax were categorised as stage III underlying destructive lung pathology. All positive cases between stages I and III were considered as stage II destructions. PTX less than 20% of ipsilateral lung surface was Grade 1 (*Figure 1*), while total PTX and those subtotal ones causing tension PTX were categorised as Grade 3. Any extension of free air collection between Grade 1 and 3 was categorised as Grade 2. The PM group was treated as a separate entity (*Figure 2*). Iatrogenic PTX was excluded from the study.

Statistical analysis

IBM SPSS 28 statistical software served data analysis. Descriptive analysis of the database was performed using the frequency function. Differentiating between the groups with or without previous lung pathology, Kruskal-Wallis test was used to determine whether there was a statistically

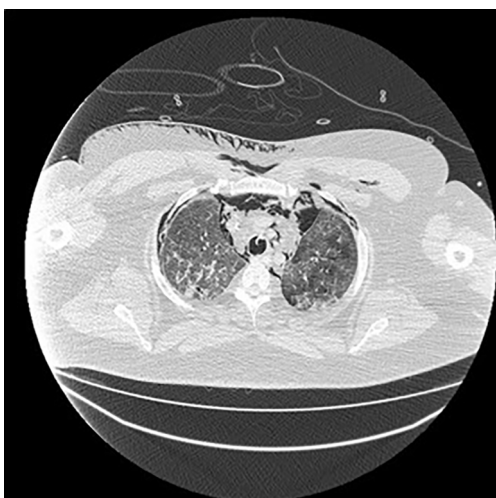


Figure 2 Pneumomediastinum.

Table 1 Descriptive statistics: the age of the studied population

Variables	Values
N	60
Mean (years)	65.48
Median (years)	67.50
Mode (years)	66
Standard deviation (years)	10.881
Minimum (years)	31
Maximum (years)	85

significant difference in the development of PTX/PM between groups. Spearman correlation tested the connection between previous lung pathology and onset of PTX/PM. We performed logistic regression analysis to determine how the co-presence of age, sex, previous lung pathology, mechanical ventilation (MV)/non-invasive ventilation (NIV) variables affect PTX/PM as an outcome. Cox-regression analysis was executed to see how the presence of different previous lung pathology groups influence the days needed to develop PTX/PM in patients.

Results

The mean age of the 60 patients was 65.48 years, the median was 67.50 years (range, 31–85 years). The sex ratio was 75–25% in favour of men (Table 1). Table 2 summarises the PTX/PM cases compared to pre-existing lung status,

stages of pathology and grade of PTX of the patients. Of the 60 patients, 44 were those who required controlled MV via endotracheal tube, whereas 16 pressure supported ventilation via full face mask (NIV) (Table 3). Altogether 13 patients developed PTX. Descriptive statistics by age showed that the mean age of men and women was similar (65.76 vs. 64.76 years). Pre-existing lung pathology was more prevalent in older patients, with an average age of 70.24 years, compared to 63.60 years for patients without lung pathology. The average age of the patients with controlled ventilation was 66.98 years, while the average age of the group with supported ventilation was 61.38 years. The difference in mean age narrowed when the onset of PTX/PM was examined: among those with injured visceral pleura integrity it was 66.31 years, compared to 65.26 years in the group without PTX/PM (Table 4). There was a male predominance in terms of existing lung pathology, with only 2 women for every 15 men, although this could be explained by the fact that there were more men in the study. PTX/PM developed in 27.3% of our patients. Among patients with pre-existing chronic lung pathology, 58.8% required controlled MV with intubation, and only 17.6% developed PTX/PM (Tables 5,6).

In the subgroups of patients with and without underlying lung pathology, the occurrence of PTX or PM were 16.16% vs. 23.25% respectively. Survival rates for previously “healthy-lung” COVID-19 sufferers were 37.20% opposed to the 22.22% for stage III pre-existing lung pathology.

The results of the Kruskal-Wallis test showed that there was no statistically significant difference ($P < 0.05$) between the different PTX stages [1, 2, 3] and the development of PM in patients with previous lung pathology ($P = 0.673$). In other words, it did not matter which group the patient belonged to in terms of PTX development. Spearman correlation did not show a statistically significant association between pre-existing chronic lung pathology and the development of PTX stages and PM ($r = -0.098$, $P = 0.456$). The Cox regression did not show a statistically significant result when examining how pre-existing lung pathology affect the time to onset of PTX ($P = 0.602$) (Table 7).

Logistic regression did not yield statistically significant results for any of the variables when analysed together with age, sex, ventilation mode, and the size of lung pathology (Figure 3). The model included age, sex, MV/NIV ventilatory strategy, and chronic pre-existing lung pathology. The model produced was calculated by SPSS to reflect reality ($P < 0.001$), and the predictive value of the model was 78.3%. The lowest odds ratio was obtained

Table 2 PTX/PM vs. pre-existing lung status

PTX vs. lung status	No pre-existing pathology	Stage I, destroyed lung <10%	Stage II, destroyed lung 10–50%	Stage III, destroyed lung >50%	Total
No PTX	33	3	1	10	47
Grade 1 PTX	1	1	0	0	2
Grade 2 PTX	4	0	0	1	5
Grade 3 PTX	1	1	0	0	2
PM	4	0	0	0	4
Total	43	5	1	11	60

PTX, pneumothorax; PM, pneumomediastinum.

Table 3 Descriptive statistics: variables of the studied population

Variables	Groups	Number	Percent (%)
Sex	Male	45	75.0
	Female	15	25.0
Pathology	Yes	17	28.3
	No	43	71.7
Ventilation	MV	44	73.3
	NIV	16	26.7
PTX/PM	Yes	13	21.7
	No	47	78.3
Survival	Exit	41	68.3
	Alive	19	31.7

PTX, pneumothorax; PM, pneumomediastinum; MV, mechanical ventilation; NIV, non-invasive ventilation.

for the age variable however, the result is statistically not significant [odds ratio (OR) =1.001, 95% confidence interval (95% CI): 0.937–1.068, P=0.985]. The odds ratio for lung pathology was 1.209, but the results are also not significant (95% CI: 0.597–2.450, P=0.598). The odds ratio for sex was 1.356 with a confidence interval of 0.304–6.047, which is statistically not significant (P=0.689). For ventilation, we obtained the highest odds ratio of 5.221 with a confidence interval of 0.562–48.515 and the lowest significance value but it was also statistically not significant (P=0.146) (*Figure 3*).

Discussion

Our hypothesis, that the increased number of PM and

secondary PTX in ventilated COVID-19 patients has a relationship with pre-existing lung pathology was not confirmed.

While barotrauma induced PTX and PM is a well-known, but rare phenomenon in ventilated ARDS patients (18), a stark increase in PTX and PM have been observed from the beginning of the SARS-COVID-19 second pandemic wave, between March 2020 and March 2021 in Hungary (19). The COVID-19 PTXs observed by us and reported by others (20,21) seem to represent a distinctively specific pattern, a different situation. In an ordinary spontaneous PTX situation, the apex of the lung is expected to come down first, followed by the lateral surface. Lung parenchyma shrinkage due to viral inflammation consolidation rather than true intrapleural pressure compression is the main cause of PTX when it is circumferential (Grade 3 PTX). Our experience of lack of significant amount of air escape at the very time of drainage supports this hypothesis.

The lack of expected increase of frequency in PTX/PM among patients with pre-existing chronic lung parenchyma pathologies might be offered by two, mutually not exclusive explanations. The first, mechanical approach might be based on an increased resilience against pressure trauma as the dominance of the fibrotic elements. A similar pattern was recently identified in blunt liver trauma (22).

The second explanation is in a need of revisiting the mechanism leading to the PTX itself. Bullous part of visceral pleura is considered as a weak area, breaking point during ventilation. A reasonable explanation for the air escape is offered by the localised vascular necrosis of the external layer of the coat of the lung. The surgical finding of one of the resected bullae being rotten (23) supports this hypothesis. Venous micro thrombosis, capillary

Table 4 Descriptive statistics by age

Variables	Number	Mean (years)	Median (years)	Mode (years)	Std. deviation (years)	Minimum (years)	Maximum (years)
Male	45	65.76	69.00	69	10.971	31	79
Female	15	64.67	66.00	66	10.939	47	85
Pathology: yes	17	70.24	70.00	66	6.897	54	79
Pathology: no	43	63.60	66.00	66	11.638	31	85
Ventilation: MV	44	66.98	68.50	66	9.559	42	85
Ventilation: NIV	16	61.38	64.00	31	13.386	31	78
PTX + PM: yes	13	66.31	70.00	31	15.966	31	85
PTX + PM: no	47	65.26	67.00	66	9.225	44	79

MV, mechanical ventilation; NIV, non-invasive ventilation; Std., standard; PTX, pneumothorax; PM, pneumomediastinum.

Table 5 Descriptive statistics by pre-existing lung pathology ventilation strategy

Pathology	Sex, n (%)			MV/NIV, n (%)			PTX/PM, n (%)		
	Male	Female	Total	Yes	No	Total	Yes	No	Total
Yes	15 (88.2)	2 (11.8)	17 (100.0)	10 (58.8)	7 (41.2)	17 (100.0)	3 (17.6)	14 (82.4)	17 (100.0)
No	30 (69.8)	13 (30.2)	43 (100.0)	34 (79.1)	9 (20.9)	43 (100.0)	10 (23.3)	33 (76.7)	43 (100.0)

MV, mechanical ventilation; NIV, non-invasive ventilation; PTX, pneumothorax; PM, pneumomediastinum.

Table 6 Descriptive statistics by ventilation strategy

Ventilation	Sex, n (%)			PTX/PM, n (%)		
	Male	Female	Total	Yes	No	Total
MV	32 (72.7)	12 (27.3)	44 (100.0)	12 (27.3)	32 (72.7)	44 (100.0)
NIV	13 (81.3)	3 (18.8)	16 (100.0)	1 (6.3)	15 (93.8)	16 (100.0)

PTX, pneumothorax; PM, pneumomediastinum; MV, mechanical ventilation; NIV, non-invasive ventilation.

Table 7 Summary of the complex statistical analysis of the study population

Statistical analysis	P	r	HR	95% CI
Kruskal-Wallis Test	0.673	–	–	–
Spearman correlation	0.456	–0.098	–	–
Cox regression	0.602	–	0.808	0.364–1.797

HR, hazard ratio; CI, confidence interval.

wall thickening is a proven consequence of COVID-19 infection, a phenomenon leading to wet necrosis, hence the cited rotten bulla.

Whatever is the mechanism of the intrapleural accumulation of the air, the lateral lung surface tends to be tethered to the parietal pleura in all but the Grade 3

PTX cases. The mediastinal face of the visceral pleura remains relatively free due to the permanent movement of the adjacent heart and great vessels providing space for developing circumscribed free air containing regions. The vessel rich hilar region, with transmitted micro vibrations of blood flow is also working against the permanent

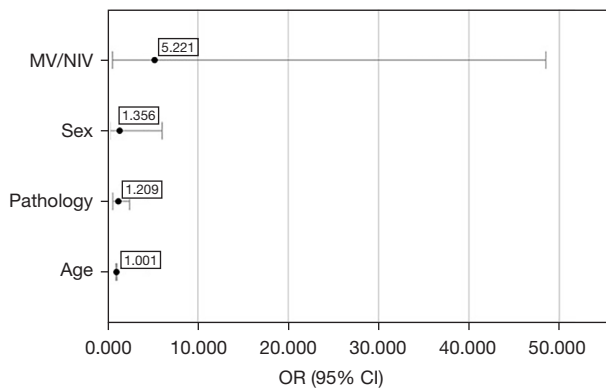


Figure 3 Logistic regression analysis of the variables. MV, mechanical ventilation; NIV, non-invasive ventilation; OR, odds ratio; CI, confidence interval.

juxtaposition needed for mediastinal-pleura symphysis. Microporous—necrotic and/or mechanical minimal ruptures are allowing air to dissect along the broncho vascular sheath. The theoretical explanations offered by Macklin (24) the air spreads along peribronchovascular sheets to the mediastinum. The barotrauma hypothesis is contradicted by the several spontaneous PTX cases without ventilation reported by other authors (25-31), and by our own biomechanical experiments (32,33): resistance of resected pleural bullae walls up to 1,938 cmH₂O against pressure is another strong evidence against barotrauma caused PTX in ventilated patients (32).

Our study also has limitations. First, this is a study using data from a single institution, and the study population is small. Therefore, higher case number or data from more centres would be beneficial. Second, the treatment protocol of PTX/PM was expert opinion based and highly individualised instead of being strictly standardised. Third, as time passed by, the treatment policy underwent a significant shift towards the less invasive ventilatory strategies, causing undesired heterogeneity in the study population.

Conclusions

In conclusion, our results suggest, that the pre-existing diffuse lung pathologies do not increase the chances of onset of PTX/PM in ventilated COVID-19 patients. What is clear, PM and PTX in these cases are primarily consequences of the viral inflammation and consequent lung consolidation, rather than direct pressure injury. The evidence provided needs further confirmation in the

alveolar barotrauma versus visceral pleura vulnerability debate sparked by the authors.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-817/rc>

Data Sharing Statement: Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-817/dss>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-817/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Regional Science and Research Ethics Committee of Petz Aladar University Teaching Hospital (No. 76-1-8/2021) and individual consent for this retrospective analysis was waived.

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