A 29-Year-Old Male with a Fatal Case of COVID-19 Acute Respiratory Distress Syndrome (CARDS) and Ventilator-Induced Lung Injury (VILI)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Smit S. Deliwala
ABCD 1 Anoosha Ponnapalli
CDEF 2 Elfateh Seedahmed
CDEF 2 Mohammed Berrou
CDEF 1 Ghassan Bachuwa
ABCDEF 2 Arul Chandran

1 Department of Internal Medicine, Michigan State University at Hurley Medical Center, Flint, MI, U.S.A.
2 Department of Internal Medicine – Division of Pulmonology/Critical Care, Michigan State University at Hurley Medical Center, Flint, MI, U.S.A.

Corresponding Author: Smit S. Deliwala, e-mail: Deliwal1@msu.edu
Conflict of interest: None declared

Patient:	**Male, 29-year-old**
Final Diagnosis:	**Acute respiratory distress syndrome (ARDS) • COVID-19 •multi organ failure/septic shock • pneumothorax**
Symptoms:	**Cough • dyspnea • fatigue • myalgia**
Medication:	**—**
Clinical Procedure:	**Mechanical ventilation • thoracentesis**
Specialty:	**Critical Care Medicine**

Objective: Unknown ethiology

Background: COVID-19 patients that develop acute respiratory distress syndrome (ARDS) "CARDS" behave differently compared to patients with classic forms of ARDS. Recently 2 CARDS phenotypes have been described, Type L and Type H. Most patients stabilize at the milder form, Type L, while an unknown subset progress to Type H, resembling full-blown ARDS. If uncorrected, phenotypic conversion can induce a rapid downward spiral towards progressive lung injury, vasoplegia, and pulmonary shrinkage, risking ventilator-induced lung injury (VILI) known as the "VILI vortex". No cases of in-hospital phenotypic conversion have been reported, while ventilation strategies in these patients differ from the lung-protective approaches seen in classic ARDS.

Case Report: A 29-year old male was admitted with COVID-19 pneumonia complicated by severe ARDS, multi-organ failure, cytokine release syndrome, and coagulopathy during his admission. He initially resembled CARDS Type L case, although refractory hypoxemia, fevers, and a high viral burden prompted conversion to Type H within 8 days. Despite ventilation strategies, neuromuscular blockade, inhalation therapy, and vitamin C, he remained asynchronous to the ventilator with volumes and pressures beyond accepted thresholds, eventually developing a fatal tension pneumothorax.

Conclusions: Patients that convert to Type H can quickly enter a spiral of hypoxemia, shunting, and dead-space ventilation towards full-blown ARDS. Understanding its nuances is vital to interrupting phenotypic conversion and entry into VILI vortex. Tension pneumothorax represents a poor outcome in patients with CARDS. Further research into monitoring lung dynamics, modifying ventilation strategies, and understanding response to various modes of ventilation in CARDS are required to mitigate these adverse outcomes.

MeSH Keywords: Coronavirus • COVID-19 • Pneumothorax • Respiration, Artificial • Respiratory Distress Syndrome, Adult • Ventilator-Induced Lung Injury

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/926136

📄 1773　　🗂 3　　📊 3　　📖 17

Background

The cluster of pneumonia cases associated with the novel coronavirus (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged from Wuhan, China and spread rapidly across continents was labeled by the World Health Organization (WHO) as a global pandemic. As of May 19, 2020, 1.5 million cases of COVID-19 were present in the United States (US), with roughly 85 400 deaths [1]. COVID-19 pneumonia seems to behave differently from other viral types of pneumonia, with large swings in respiratory functioning, inferring that not all previous practices can be adopted, and new strategies are needed to mitigate the high mortality rates (79% to 86%) seen in advanced cases [2,3]. Supplemental oxygen use was seen in 38.9% of infected patients, with 28.7% requiring mechanical ventilation and less than 1% requiring advanced therapies such as extracorporeal membrane oxygenation (ECMO); however, these numbers may likely be underrepresented with preventative measures such as social distancing and stay-at-home executive orders leading to reluctance and delay in receiving care [4]. The progression of COVID-19 to ARDS ("CARDS") represents a life-threatening sequela, with its ability to lower blood oxygenation levels and induce systemic hypoxemia and multi-organ failure [3,5]. Despite CARDS meeting the Berlin Diagnostic Criteria, its trajectory is characterized by severe hypoxemia with near-normal respiratory compliance, unlike its classic form [5,6]. Patients with CARDS can present within a broad spectrum from perceived normal breathing ("silent hypoxemia") to floored respiratory compromise with a wide array of overlapping features in between [6]. Recently, 2 CARDS phenotypes have been parsed out, Type L and Type H, with each one having its distinct pathophysiological pathway. Understanding these nuances are vital to providing appropriate treatment and avoiding sub-optimal outcomes [5]. We present a case of CARDS with subsequent sequelae and numerous challenges in management. We aim to strengthen the existing literature, explore the CARDS phenotypes, and discuss therapeutic and ventilator strategies to counteract the unique lung injury seen in COVID-19 pneumonia that progress to ARDS.

Case Report

A 29-year-old male with a history of asthma, previous gunshot wound, and obesity, presented to the hospital with dyspnea, cough, fatigue, and myalgias. He used tobacco products and worked at an auto-parts manufacturing unit. On arrival, he was febrile, tachycardic, and tachypneic requiring supplemental oxygen. He appeared ill with a high work of breathing and a productive cough. Workup revealed lymphopenia to 1.4 k/uL, thrombocytopenia to 121 000 k/uL, and an unremarkable chest radiograph (Figure 1); the patient was transferred to the intensive care unit (ICU) with a high suspicion
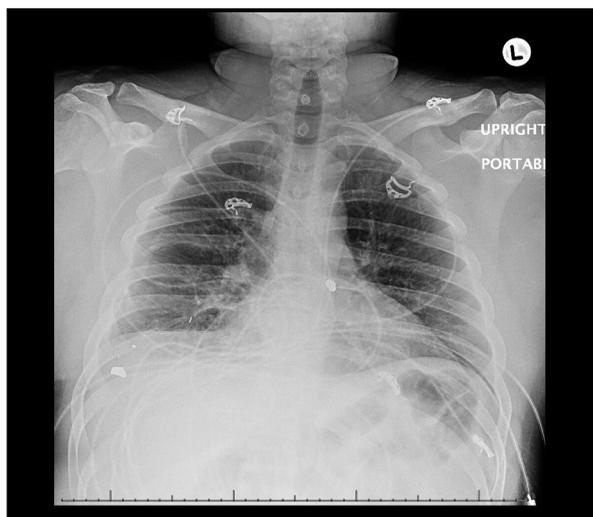
Figure 1. Chest radiograph revealing mild bilateral interstitial changes consistent with CARDS Type L on day 1.

for COVID-19. Testing for SARS-CoV-2 was completed using a nasopharyngeal swab transported in an M4 viral tube to the State Department of Health and Human Services. Samples were tested on the SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) Abbott ID NOW™ point-of-care system under the Food and Drug Administration (FDA) emergency use authorization (EUA). Computed tomography (CT) of the chest could not be performed due to concern for virus transmission and environmental contamination due to high demands and short downtime for decontamination. By day 3, the patient required higher flow rates on a non-rebreather mask, and by day 4, persistent fevers, tachypnea, and new consolidative changes in the right middle and lower lung zones were noted. He was empirically started on broad-spectrum antibiotics with hydroxychloroquine. Foregoing Bi-PAP or C-PAP due to concerns for aerosolization, he was placed on mechanical ventilation. His chest x-ray by day 8 revealed extensive consolidative infiltrates bilaterally and a PaO_2/FiO_2 (PF) ratio of 59 consistent with severe acute respiratory distress syndrome (ARDS) (Figure 2).

Testing for SARS-CoV-2 came back positive, confirming COVID-19 pneumonia. Over the following days, he went into septic shock requiring vasopressor support, while previously sent cytokine labs, including an interleukin-6 (IL-6) of 46 pg/mL, were consistent with cytokine release syndrome. He was given a dose of tocilizumab 400 mg. On day 10, extensive acute deep vein thromboses (DVTs) was discovered in his left upper extremity with d-dimer levels over 10 µg/mL. His previous prophylactic dose of enoxaparin was increased to a therapeutic dose. His fevers did not abate, requiring cooling, neuromuscular blockade, and deep sedation. ARDS strategies, including low tidal volumes, proning, recruitment maneuvers, diuretics, nitric oxide, and vitamin C, were used despite his rising pressures. During these periods, he exhibited high plateau pressures,
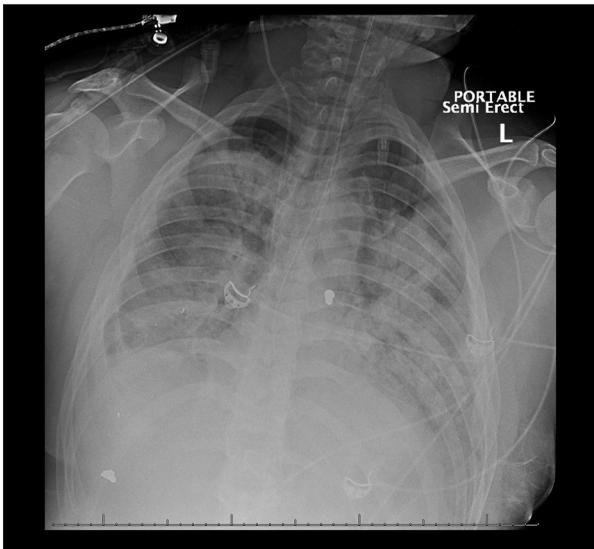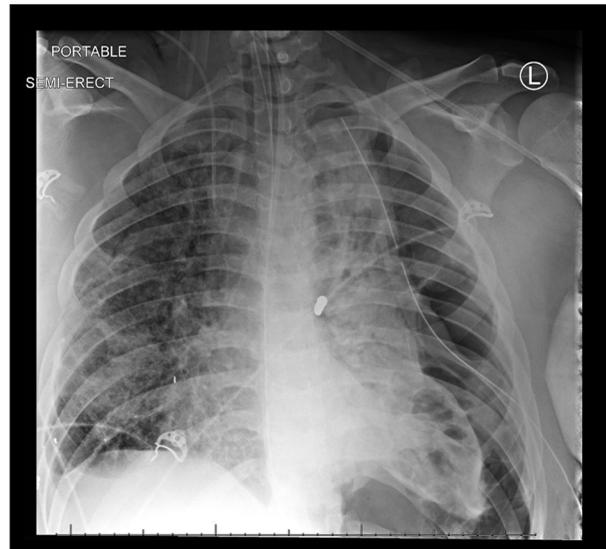
Figure 2. Chest radiograph revealing extensive bilateral consolidations consistent with CARDS Type H on day 8.

Figure 3. Chest radiograph revealing pneumothorax with near collapse of the left lung and placement of a chest tube on day 18 of admission.

often over 30 cm of H_2O. Worsening status prompted consideration of transfer to a specialized ECMO center. However, surrounding centers had limited the inflow of patients adhering to strict infection control measures, while judicious resource allocation and logistical challenges made transportation unfeasible. On day 17, after a sudden episode of desaturation, a chest x-ray revealed left-sided tension pneumothorax in the left mid and lower lung fields (Figure 3) with a chest tube draining 700 mL of serosanguineous fluid mixed with blood clots intermittently blocking output with persistent air leaks. Fluid characteristics were not obtained, and his overall clinical trajectory began declining. A family discussion was held to discuss his poor prognosis and address the goals of care. His code status was changed to do-not-resuscitate (DNR) with an emphasis on comfort measures. He eventually desaturated and went into asystole, passing away after spending 20 days in the hospital. Trends in oxygenation in our patient can be seen in Table 1.

Discussion

ARDS can be mitigated by opening collapsed alveoli with higher positive end-expiratory pressures (PEEPs), recruiting maneuvers, or proning. In contrast, these high pressures are poorly tolerated, leading to the use of low tidal volumes to minimize ventilator-induced lung injury (VILI). Despite this, high rates of barotrauma were reported from the previous SARS epidemic [7]. COVID-19 patients complicated by ARDS ("CARDS") can present despite lacking traditional risk factors such as advancing age, pre-existing co-morbidities, or an advanced lung pathology [5]. Despite the initial insult being the inoculation of SARS-CoV-2, CARDS can occur from injuries from either the gas or vascular side of the alveoli [6].

Approaching CARDS from the gas side

CARDS is defined by 2 phenotypes based on its clinical trajectory. "Type L" has a relatively compensated clinical state while "Type H" resembles full-blown ARDS (Table 2). Our patient, initially a Type L, had scattered infiltrates with rising minute ventilation over days. Type L patients are perceived to be breathing normally ("silent hypoxemia") and often respond to supplemental oxygen. At the same time, deep swings in respiration can induce patient self-inflicted lung injury (P-SILI), triggering an inflammation cascade and a rapid downward spiral towards progressive pulmonary injury and pulmonary shrinkage, known as the 'VILI vortex' towards full-blown ARDS [6]. Evidence of transformation to Type H by day 8 was noted by his rising plateau and driving pressures, lower static compliance, and low PF ratios signifying a bulkier lung. Refractory hypoxia, fevers, and systemic insults led to a dependency on high PEEPs and FiO_2 to maintain oxygen saturation above 88%.

Approaching CARDS from the vascular side

Post-mortem studies reveal numerous thromboses in COVID-19 patients with d-dimer serving as a surrogate marker of pulmonary endothelial damage, promoting ventilation-perfusion mismatches and subsequent hypoxia [5,6,8]. DVTs were noted in over 50% of patients, suggesting that coagulopathy may be an independent risk factor for poor prognosis [9]. Our patient reflected coagulopathy and vasoplegia with rising d-dimer levels in the days leading up to his DVT, while the development of cytokine release syndrome and coagulopathy signaled his growing disease burden. Once this occurs, vasoregulation is altered due to the failure of hypoxic vasoconstriction from

Table 1. Trends in oxygenation and ventilation.

Day of admission	Oxygen delivery	FiO$_2$ (%)/ flow rate (L/min)	Tidal volume (mL)	PEEP	Respira-tory rate (breaths/ min)	pH	PaO$_2$	O$_2$ satura-tion (%)	PaCO$_2$	HCO$_3$	PaO$_2$/FiO$_2$ (PF) ratio	Radiographic findings	CARDS phenotype
Day 1	Nasal cannula	2L– 6L	N/A	N/A	28–32	N/A	N/A	90	N/A	29	N/A	Mild bilateral interstitial changes (Figure 1)	Type L
Day 3	Non-rebreather	12L	N/A	N/A	34–47	N/A	N/A	90	N/A	23	N/A	Mild bilateral interstitial changes	Type L
Day 4	Volume control – Assist control	100	500	8	14	7.36	43	76.3	51	28.1	43	Interval worsening of airspace consolidation in the right mid and lower lung zone	Type L
Day 8	Volume control – Assist control	80	370	14	30	7.33	47	79.1	60	31.1	59	Bilateral extensive consolidated infiltrate concerning for multifocal pneumonia (Figure 2)	Type H
Day 13	Volume control – Assist control	100	500	20	32	7.48	118	98.5	44	32.5	118	Worsening of bilateral infiltrates. Interval development of moderate size left pleural effusion	Type H
Day 17	Volume control – Assist control	90	420	18	26	7.30	60	87.2	82	39.2	67	Interval development of moderate tension pneumothorax in left mid/lower lung field with bilateral alveolar infiltrates (Figure 3)	Type H
Day 18	Volume control – Assist control	100	450	18	32	7.38	68	92.9	61	35.1	68	Left pneumothorax with chest tube placed. Worse compared to prior with near collapse of the left lung. Left lung base consolidation	Type H

the endothelial damage resulting in significant hypoxemia. If the respiratory drive is not altered by oxygen administration, the generated inspiratory increases transpulmonary pressures across vascular channels, risking VILI. This can also serve as a learning point, that early intubation strategies can help minimize the powerful respiratory effort leading to vasoplegia. If uncorrected, high plateau pressures reflecting high trans alveolar pressures can increase thoracic compliance leading to high oxygen and PEEP requirements that can redirect blood to damaged parts with high permeability affecting hemodynamics and contributing to Type H conversion.

Pneumothorax in CARDS lungs

The accepted thresholds for VILI protection include a plateau pressure of 30 cmH$_2$O and a driving pressure of 15 cmH$_2$O [10]. Protecting CARDS lungs involves aspects of lung-protective ventilation while ensuring that the vascular side of the alveoli does not incur further damage. Oxygen strategies in these patients are summarized in Table 3. Surrogate measures to monitor work of breathing have been proposed and may help guide therapy with esophageal manometry for inspiratory or central venous pressure (CVP) swings. At the same time, interrupters of the VILI vortex include early intubation, sedation, or paralysis with the use of lower PEEP (8–10 cmH$_2$O) [6,11]. After consistently cycling through the VILI vortex, our patient

Table 2. Characteristics of COVID-19 pneumonia (CARDS) Type L and H.

COVID-19 Pneumonia, Type L	Property	COVID-19 Pneumonia, Type H
Low	Elastance	High
Normal-to-high	Compliance	Low
Normal	Gas volume	Decreased
Low ventilation-to-perfusion (V/Q) ratio due to vasoplegia and loss of hypoxic vasoconstriction	Primary driver of hypoxia	Right-to-left shunt due to perfusion of non-aerated regions affected by edema and high pressures
Normal-to-low	Lung weight	High
Low with sparse non-aerated regions	Lung recruitability/PEEP response	Increased with more non-aerated regions
Limited interstitial ground-glass opacities along subpleural planes and lung fissures	Computed tomography (CT)	Extensive consolidations

Table 3. Oxygen strategies in COVID-19 pneumonia (CARDS) Type L and Type H.

COVID-19 Pneumonia, Type L	Time Frame	COVID-19 Pneumonia, Type H
Nasal cannula, high-flow nasal cannula, continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation (NIPPV), or awake proning to avoid increased respiratory efforts	Pre-intubation	Nasal cannula, high-flow nasal cannula, continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation (NIPPV), or awake proning to avoid increased respiratory efforts
Lower positive end-expiratory pressures (PEEP) (<10 cmH$_2$O), tidal volumes (7–9 mL/kg), maintain gas exchange and fluid balances. Proning only as a rescue maneuver. extracorporeal membrane oxygenation (ECMO) in severe COVID-19 patients	Mechanical ventilation	Higher positive end-expiratory pressures (PEEP) (<15 cmH2O), tidal volumes (5–7 mL/kg), maintain gas exchange and fluid balances. Initiate proning and extracorporeal membrane oxygenation (ECMO) if parameters met. Manage these patients as full-blown ARDS
Avoid vigorous spontaneous increases in breathing, pressure swings with breathing trials towards the ending of the weaning process. The goal is to avoid ventilator-induced lung injury (VILI) and worsening edema. Initiate careful weaning measures	Weaning	Avoid vigorous spontaneous increases in breathing, pressure swings with breathing trials towards the ending of the weaning process. The goal is to avoid ventilator-induced lung injury (VILI) and worsening edema. Initiate careful weaning measures

developed spontaneous pneumothorax with a 50% drop in his PF ratio because of his high plateau pressures, respiratory swings, and inflammation. The incidence of pneumothorax has been reported to be roughly 6% in COVID-19 patients [12], although these represented spontaneous cases from the community, unlike our case which was a consequence of progressive lung injury and the inability to liberate the patient from the VILI vortex. The development of pneumothorax after intubation can portend a poor prognosis in patients with CARDS [12–14].

Importance of categorizing CARDS lungs

Categorizing lung injury from COVID-19 into CARDS Type L or Type H can help unwanted practices and initiate targeted

ventilator approaches to correct the underlying mismatch. The Surviving Sepsis Campaign recommended that mechanically ventilated COVID-19 patients be managed similarly to other patients with respiratory failure in the ICU, although with the growing body of evidence, CARDS is displaying a distinct course [15]. The 3 essential contributors to CARDS and entry into the VILI vortex are 1) SARS-CoV-2 burden, 2) ventilator responsiveness, and 3) time of symptom onset [6]. The paucity of reported cases brings into light the importance of isolated reports in guiding therapy in the current climate. This case represents the first reported CARDS patient that developed a pneumothorax as a consequence of his phenotype conversion. In previous cases of SARS patients, pneumothorax was noted at 14–37 days after the initial diagnosis [16], suggesting that

a sustained period of lung inflammation serves as a pre-requisite, a similar time course as our patient Recently a scoring system was proposed to predict the risk of developing critical illness in COVID-19, allowing early interventions and resource allocation to mitigate the high disease burden [17].

Conclusions

COVID-19 patients that develop ARDS ("CARDS") come in 2 phenotypes: Type L and H. Type L is often stable while Type H presents like full-blown ARDS. These patients require different ventilator strategies with the goal of avoiding conversion to Type H and limiting VILI. In these cases, pneumothorax may represent an indicator of a poor outcome.

Conflict of interests

None.

References:

1. Dong E, Du H, Gardner L: An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis, 2020; 20: 533-34

2. Dondorp AM, Hayat M, Aryal D et al: Respiratory support in novel coronavirus disease (COVID-19) patients, with a focus on resource-limited settings. Am J Trop Med Hyg, 2020; 102: 1191–97

3. Geier MR, Geier DA: Respiratory conditions in coronavirus disease 2019 (COVID-19): important considerations regarding novel treatment strategies to reduce mortality. Med Hypotheses, 2020; 140: 109760

4. de Simone G, Mancusi C: COVID-19: Timing is important. Eur J Intern Med, 2020 [Online ahead of print]

5. Marini JJ, Gattinoni L: Management of COVID-19 respiratory distress. JAMA, 2020; 7(6): 435–44

6. Gattinoni L, Chiumello D, Caironi P et al: COVID-19 pneumonia: Different respiratory treatments for different phenotypes? Intensive Care Med, 2020; 46: 1099–102

7. Fowler RA: Critically ill patients with severe acute respiratory syndrome. JAMA, 2003; 290: 367–73

8. Rello J, Storti E, Belliato M, Serrano R: Clinical phenotypes of SARS-CoV-2: Implications for clinicians and researchers. Eur Respir J, 2020; 55: 2001028

9. Wichmann D, Sperhake J-P, Lütgehetmann M et al: Autopsy findings and venous thromboembolism in patients with COVID-19. Ann Intern Med, 2020 [Online ahead of print]

10. Tonetti T, Vasques F, Rapetti F et al: Driving pressure and mechanical power: New targets for VILI prevention. Ann Transl Med, 2017; 5(14): 286

11. Walling Pt, Savege Tm: A comparison of oesophageal and central venous pressures in the measurement of transpulmonary pressure change. Br J Anaesth, 1976; 48(5): 475–79

12. Yao W, Wang T, Jiang B et al: Emergency tracheal intubation in 202 patients with COVID-19 in Wuhan, China: Lessons learnt and international expert recommendations. Br J Anaesth, 2020 [Online ahead of print]

13. Rohailla S, Ahmed N, Gough K: SARS-CoV-2 infection associated with spontaneous pneumothorax. CMAJ, 2020; 2020: E510

14. Wang W, Gao R, Zheng Y, Jiang L: COVID-19 with spontaneous pneumothorax, pneumomediastinum and subcutaneous emphysema. J Travel Med, 2020 [Online ahead of print]

15. Alhazzani W, Møller MH, Arabi YM et al: Surviving sepsis campaign: Guidelines on the management of critically ill adults with Coronavirus disease 2019 (COVID-19). Intensive Care Med, 2020; 46(5): 854–87

16. Sihoe ADL, Wong RHL, Lee ATH et al: Severe acute respiratory syndrome complicated by spontaneous pneumothorax. Chest, 2004; 125(6): 2345–51

17. Liang W, Liang H, Ou L et al: Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. JAMA Intern Med, 2020 [Online ahead of print]