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Perspective

It is time to update the ARDS definition: It starts with COVID-19-induced respiratory failure☆

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ABSTRACT

Coronavirus disease 2019 (COVID-19) may rapidly worsen respiratory failure, thereby leading to death. COVID-19-induced respiratory failure exhibits some atypical characteristics, silent hypoxemia, and high lung compliance. Some histopathological changes associated with COVID-19-induced respiratory failure differ from those of classic acute respiratory distress syndrome (ARDS). However, compared with classical ARDS, COVID-19-induced respiratory failure has a similar timing of onset, clinical syndromes, radiological profile, and mortality rate in the intensive care unit (ICU). Respiratory failure induced by COVID-19 is a type of ARDS and is currently underdiagnosed. This condition stretches the definition of classic ARDS; therefore, an updated definition is warranted.

Introduction

Up to June 2020, the coronavirus disease 2019 (COVID-19) pandemic had caused >1 million deaths worldwide.[1,2] COVID-19 may rapidly worsen respiratory failure, thereby leading to death.[3] COVID-19-induced respiratory failure exhibits some atypical characteristics: (1) some patients with COVID-19 have relatively normal lung compliance; and (2) pulmonary thrombosis and local vasodilation are common in COVID-19. Therefore, some experts think that COVID-19-induced respiratory failure is not an acute respiratory distress syndrome (ARDS). However, compared with classical ARDS, COVID-19-induced respiratory failure has a similar timing of onset, clinical syndromes, radiological profile, histological changes, and mortality in the intensive care unit (ICU). Respiratory failure induced by COVID-19 is a type of ARDS and is currently underdiagnosed. This condition stretches the definition of classic ARDS; therefore, an updated definition is warranted.

Timing of Onset

According to the Berlin definition, the timing of onset is defined as the appearance of an established clinical insult or new or worsening respiratory symptoms within 1 week.[4] This definition refers to normal causes of ARDS, which can be easily recognized. However, the timing of onset of COVID-19-induced respiratory failure cannot be easily recognized because the time of infection and latent period are unclear. The time course for the occurrence of symptoms in ARDS is used to evaluate the timing of onset in COVID-19. Recent studies in Wuhan, China, showed that the time course for the occurrence of symptoms in ARDS for COVID-19 was 12 days (interquartile range [IQR]: 8–15 days); however, the syndrome was underdiagnosed during the early days of the pandemic.[5] In the USA, the median time from symptom onset to need for invasive mechanical ventilation (IMV) was 8 days (IQR: 6–10 days), and the median time to IMV after admission was 1 day (IQR: 0–3 days).[6] In Italy, the median time from symptom onset to need for IMV was 8 days (IQR: 6–10 days).[7] Although IMV cannot fully represent the occurrence of ARDS, the timing of onset of COVID-19-induced ARDS appears to be similar to that of classic ARDS.

Atypical Respiratory Distress

Patients with severe COVID-19 have hypoxemia and/or hypercapnia. However, unlike in classic ARDS, some COVID-19 patients with hypoxemia do not have respiratory distress.

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At the onset, the clinical symptoms of COVID-19 are fever, dry cough, and dyspnea.[8,9] Nevertheless, the specific phenomenon of "silent hypoxia" or "silent hypoxemia" has also been observed in patients with COVID-19.[10–12] At the initial stage of the COVID-19 outbreak, Dr Haibo Qiu noticed that some patients tolerated the extremely low levels of blood oxygen content well (e.g., saturation of oxygen: 70–80%; partial pressure of oxygen: 30–40 mmHg). However, the patient's condition markedly deteriorates following mild-to-moderate physical activities, such as getting out the bed, excessive coughing, straining during urination or defecation, etc.[13] The mechanisms involved in this process may be associated with focal lung injury and high respiratory compliance.[14]

Not All Have Low Respiratory Compliance

Based on the mechanisms of impaired blood-gas exchange, the clinical phenotypes can be divided into Type L and Type H. Type L is characterized by low elastance, low ventilation-to-perfusion ratio, low lung weight, and low lung recruitability. Type H is characterized by high elastance, high right-to-left shunt, high lung weight, and high lung recruitability.[12]

Type L is a pseudo-normality of lung mechanics; nevertheless, it is associated with severe damage to the lungs. COVID-19 patients with Type L or Type H have hypoxemia. However, Type L is characterized by preserved lung aeration and high lung compliance. In addition, the transpulmonary pressures with mechanical ventilation remain below the thresholds commonly referred to as harmful.[15,16] Gattinoni et al.[17] found that in 12 patients with COVID-19, a respiratory system compliance of 52.1 ± 15.4 mL/cm H_2O was associated with a shunt fraction of 0.51 ± 0.10. Similar changes in pathophysiology were observed in the study conducted by Mauri et al.[18] In 25 patients with COVID-19, the dead space ranged 6–41% and the shunt fraction was 5–37%. In a multicenter study, patients with COVID-19 had high respiratory system compliance *vs.* those with classic ARDS; however, the lung weight in patients with COVID-19 was similar to that measured in patients with classic ARDS.[14] Such a wide discrepancy is not commonly observed among most forms of ARDS.

Based on the observation of unmatched hypoxemia and hypercapnia,[13,19] researchers have hypothesized the involvement of several mechanisms. First, COVID-19-induced lung injury is characterized by lung inhomogeneity, alveolar collapse in injured lung tissues, alveolar hyperinflation, and vessel diastole abnormality in normal lung tissues. These effects lead to ventilation/perfusion mismatch and an increase in dead space. Second, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces abnormal vasodilatation of the injured pulmonary tissues, which increases the local shunt and leads to hypoxemia. Third, combined with the remarkably high incidence of thrombotic complications, recent reports of increased respiratory dead space suggest the occurrence of lung-vascular thrombosis due to thrombotic microangiopathy or pulmonary embolism was ≤40% of hospitalized patients with COVID-19.[20–22] We strongly suspect that these mechanisms are the main culprit for impaired blood-gas exchange in COVID-19.

Silent hypoxemia and Type L are specific clinical features of COVID-19. However, the symptoms may be the early manifestation of ARDS; for classic ARDS, the symptoms may be ignored.

Histopathological Changes

Histopathological changes in COVID-19 are similar to those noted in classic ARDS. It was retrospectively found that two patients with early-phase COVID-19 pneumonia who underwent lung lobectomy for adenocarcinoma had COVID-19 at the time of the operation. Pathologic examinations revealed that the lungs exhibited edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cell infiltration, and multinucleated giant cells.[23] In a case series, the major pulmonary finding was diffuse alveolar damage in the acute or organizing phases, which was evidenced by the presence of intra-alveolar fibrin, hyaline membranes, or loosely organizing connective tissue in the alveolar septal walls. Most patients showed variable degrees of chronic interstitial inflammation, with some having more prominent perivascular lymphocytic and neutrophilic inflammation.[24]

Coagulopathy is an important complication of COVID-19 infection.[24,25] Microthrombi have been found in the lungs, trachea, and kidneys of some patients. Focal pulmonary microthrombi increase the dead space and shunt, which lead to hypoxemia and hypercapnia, as well as and worsening of patients' condition. Moreover, in SARS-CoV-2 induced coagulopathy, microthrombi are also linked to hemoconcentration caused by fever, less food intake, and loss of digestive tract, etc. Except for coagulation abnormalities, the histopathological changes caused by COVID-19 are similar to those of classic ARDS; hence, the coagulation abnormalities should attract the attention of clinicians.

Mortality

In the early phase of the COVID-19 pandemic, due to the lack of medical supplies, the mortality rate in Wuhan was 43%,[5,8] the ICU mortality rate among patients in Metropolitan Detroit (MI, USA) was 40.4%,[6] and the all-cause hospital mortality rate in a University tertiary care hospital in northern Italy was 43.6%.[7] In the USA, the in-hospital mortality rate was highest in the early phase and decreased (from 18.5% to 10.8%) as healthcare staff gained experience in treating patients with COVID-19.[26] The mortality rate in COVID-19-induced ARDS is similar to that recorded in classic severe ARDS.[5,27]

COVID-19-induced ARDS causes some changes which differ from those associated with classic ARDS. Thus, some experts suggested that COVID-19-induced respiratory failure is not ARDS.[28] For the new infectious disease of COVID-19, we have witnessed the entire clinical course of patients with COVID-19 from viral infection to onset and aggravation. However, in most cases, we cannot observe the entire course of classic ARDS. Therefore, although the very early phase of COVID-19 exhibits special clinical features, the timing of onset, radiological profile, histopathological changes, and mortality rate are similar to those of classic ARDS.

Based on this evidence, COVID-19 expands the clinical manifestations, pathophysiology, and histopathological changes linked to ARDS. Hence, it is time to update the definition of ARDS.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8(5):475–81. doi:10.1016/S2213-2600(20)30079-5.
[2] WHO. WHO coronavirus disease (COVID-19) dashboard. 2020. Available from: https://covid19.who.int/.
[3] Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with different severities: a multicenter study of clinical features. Am J Respir Crit Care Med 2020;201(11):1380–8. doi:10.1164/rccm.202002-0445OC.
[4] Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307(23):2526–33. doi:10.1001/jama.2012.5669.
[5] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054–62. doi:10.1016/S0140-6736(20)30566-3.
[6] Suleyman G, Fadel RA, Malette KM, Hammond C, Abdulla H, Entz A, et al. Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in metropolitan detroit. JAMA Netw Open 2020;3(6):e2012270. doi:10.1001/jamanetworkopen.2020.12270.
[7] Vena A, Giacobbe DR, Di Biagio A, Mikulska M, Taramasso L, De Maria A, et al. Clinical characteristics, management and in-hospital mortality of patients with coronavirus disease 2019 in Genoa, Italy. Clin Microbiol Infect 2020;26(11):1537–44. doi:10.1016/j.cmi.2020.07.049.
[8] Xie J, Wu W, Li S, Hu Y, Hu M, Li J, et al. Clinical characteristics and outcomes of critically ill patients with novel coronavirus infectious disease (COVID-19) in China: a retrospective multicenter study. Intensive Care Med 2020;46(10):1863–72. doi:10.1007/s00134-020-06211-2.
[9] Vena A, Giacobbe DR, Di Biagio A, Mikulska M, Taramasso L, De Maria A, et al. Clinical characteristics, management and in-hospital mortality of patients with coronavirus disease 2019 in Genoa, Italy. Clin Microbiol Infect 2020;26(11):1537–44. doi:10.1016/j.cmi.2020.07.049.
[10] Xie J, Tong Z, Guan X, Du B, Qiu H, Slutsky AS. Critical care crisis and some recommendations during the COVID-19 epidemic in China. Intensive Care Med 2020;46(5):837–40. doi:10.1007/s00134-020-05979-7.
[11] Ottestad W, Søvik S. COVID-19 patients with respiratory failure: what can we learn from aviation medicine. Br J Anaesth 2020;125(3):e280–1. doi:10.1016/j.bja.2020.04.012.
[12] Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes. Intensive Care Med 2020;46(6):1099–102. doi:10.1007/s00134-020-06033-2.
[13] Couzin-Frankel J. The mystery of the pandemic's 'happy hypoxia. Science 2020;368(6490):455–6. doi:10.1126/science.368.6490.455.
[14] Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med 2020;8(12):1201–8. doi:10.1016/S2213-2600(20)30370-2.
[15] Grieco DL, Chen L, Brochard L. Transpulmonary pressure: importance and limits. Ann Transl Med 2017;5(14):285. doi:10.21037/atm.2017.07.22.
[16] Viola L, Russo E, Benni M, Gamberini E, Circelli A, Bissoni L, et al. Lung mechanics in type L CoVID-19 pneumonia: a pseudo-normal ARDS. Transl Med Commun 2020;5(1):27. doi:10.1186/s41231-020-00076-9.
[17] Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med 2020;201(10):1299–300. doi:10.1164/rccm.202003-0817LE.
[18] Mauri T, Spinelli E, Scotti E, Colussi G, Basile MC, Crotti S, et al. Potential for lung recruitment and ventilation-perfusion mismatch in patients with the acute respiratory distress syndrome from coronavirus disease 2019. Crit Care Med 2020;48(8):1129–34. doi:10.1097/CCM.0000000000004386.
[19] Pan C, Chen L, Lu C, Zhang W, Xia JA, Sklar MC, et al. Lung recruitability in COVID-19-associated acute respiratory distress syndrome: a single-center observational study. Am J Respir Crit Care Med 2020;201(10):1294–7. doi:10.1164/rccm.202003-0527LE.
[20] Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145–7. doi:10.1016/j.thromres.2020.04.013.
[21] Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost 2020;18(7):1743–6. doi:10.1111/jth.14869.
[22] Léonard-Lorant I, Delabranche X, Séverac F, Helms J, Pauzet C, Collange O, et al. Acute pulmonary embolism in patients with COVID-19 at CT angiography and relationship to D-dimer levels. Radiology 2020;296(3):E189–91. doi:10.1148/radiol.2020201561.
[23] Tian S, Hu W, Niu L, Liu H, Xu H, SY X. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol 2020;15(5):700–4. doi:10.1016/j.jtho.2020.02.010.
[24] Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. Lancet 2020;396(10247):320–32. doi:10.1016/S0140-6736(20)31305-2.
[25] Hanley B, Naresh KN, Roufosse C, Nicholson AG, Weir J, Cooke GS, et al. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. Lancet Microbe 2020;1(6):e245–53. doi:10.1016/S2666-5247(20)30115-4.
[26] Mulhem E, Oleszkowicz A. Lick D. 3219 hospitalised patients with COVID-19 in Southeast Michigan: a retrospective case cohort study. BMJ Open 2021;11(4):e042042. doi:10.1136/bmjopen-2020-042042.
[27] Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315(8):788–800. doi:10.1001/jama.2016.0291.
[28] Li X, Ma X. Acute respiratory failure in COVID-19: is it "typical" ARDS. Crit Care 2020;24(1):198. doi:10.1186/s13054-020-02911-9.