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Perspective

An expanded definition of acute respiratory distress syndrome: Challenging the *status quo*

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Acute respiratory distress syndrome (ARDS) is a severe form of acute hypoxic respiratory failure caused by non-cardiogenic pulmonary edema.[1] Since it was first described 50 years ago, the definition of ARDS has been revised several times to match the needs of patients, clinicians, and investigators. Following the 1988 proposal for an acute lung injury score and the 1994 American-European Consensus Conference definition, the Berlin definition of ARDS, 2012 recommended that the term should encompass patients with acute onset (1 week from a clinical insult), requiring positive end-expiratory pressure (PEEP) of at least 5 cm H_2O, and bilateral infiltrates on chest radiography that are not caused by heart failure; it categorized severity based on the arterial oxygen tension(PaO_2)/inspired oxygen fraction(FiO_2) ratio.[2] Nonetheless, issues have occasionally been raised regarding various criteria of the Berlin definition since it was proposed and widely used in clinical practice and research. Notably, the definitions of clinical syndromes are not universal and should be reviewed periodically. Certain new considerations regarding the definition of ARDS are therefore being raised.

Issue 1: Should Patients with High-Flow Nasal Oxygen (HFNO) be Included?

HFNO is widely used as an alternative to conventional oxygen therapy and non-invasive ventilation (NIV) in patients with acute hypoxemic respiratory failure, as it is associated with lower 90-day mortality.[3] Despite the lack of confirmatory evidence on the benefits related to mortality or other clinical outcomes, HFNO has recently become an integral part of non-invasive respiratory support in COVID-19 patients.[4–6] HFNO offers certain physiological advantages; these include maintenance of a modest flow-dependent level of PEEP (2–5 cm H_2O), reduction of dead space owing to flushing of the upper airways, and reduction in the work of breathing.[7–10] Although HFNO is widely used to support patients with bilateral pulmonary infiltrates and severe hypoxemia (PaO_2/FiO_2 ratio <300 mmHg), these patients are not diagnosed with ARDS as they do not receive positive-pressure ventilation with a PEEP of at least 5 cm H_2O.

As HFNO is routinely used in clinical practice, there is increasing debate regarding the expansion of the Berlin ARDS definition to include HFNO. Existing arguments in favor of broadening the ARDS definition to include patients requiring HFNO are based on the following factors:

(1) Non-ventilated patients who otherwise meet the Berlin criteria have similar clinical characteristics, biomarkers of inflammation, and outcomes as those with ARDS.[11,12] A pivotal study found that non-ventilated patients who met all other criteria for ARDS had the same 60-day mortality as those who were ventilated.[11] Another study showed that patients with acute hypoxemia and bilateral opacities treated with HFNO had similar patterns of inflammation and injury-related biomarkers as ARDS patients who were mechanically ventilated.[12] HFNO, which is more readily available than invasive mechanical ventilation (MV) and NIV, can generate sufficient PEEP (near 5 cm H_2O) at a high flow rate. Parke et al.[13] measured the nasopharyngeal pressure in patients undergoing cardiac surgery and found that HFNO with a flow rate of 50 L/min delivered a mean ±standard deviation airway pressure of 3.31 ± 1.05 cm H_2O with the mouth closed.

(2) Most patients fulfilling other ARDS criteria during HFNO still fulfill ARDS criteria after intubation. In a recent study, Ranieri et al.[6] found that the PaO_2/FiO_2 ratio of ≤300 mmHg on HFNO was sustained in 92.9% of patients despite invasive MV. A concurrent study revealed that most patients with bilateral opacities and a PaO_2/FiO_2 value of ≤300 mm Hg under standard oxygen inhalation fulfilled the Berlin criteria within the first 24 h.[14] Based on all the above evidence, positive pressure ventilation does not appear to be

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a prerequisite for the diagnosis of ARDS. Furthermore, the criteria of the Berlin definition focus on disease status instead of treatment. Including patients receiving HFNO in the ARDS definition may therefore facilitate early identification and intervention. However, stricter evidence-based parameters are needed to avoid over broadening of the diagnosis of ARDS; in this context, the lack of unified strict standards for clinical conditions and parameters of HFNO may increase the risk of overexpansion. Matthay et al.[15] recommended that the requirement for HFNO of at least 30 L/min should be added as a criterion for the diagnosis of ARDS. Further research is needed to validate this view.

Issue 2: Should oxygen saturation (SpO_2)/FiO_2 be an Alternative to PaO_2/FiO_2 for the Diagnosis of ARDS?

Clinician under-recognition of ARDS has long been a concern, and only 60.2% of patients with ARDS can be identified by clinicians.[16] Unavailability of the PaO_2/FiO_2 ratio, the cornerstone of ARDS diagnosis, may contribute to the under-diagnosis of the condition. Notably, the SpO_2/FiO_2 ratio has been found to be closely associated with the PaO_2/FiO_2 ratio, which may allow a non-invasive diagnosis of ARDS, especially in resource-constrained settings; use of the latter may prevent under diagnosis of ARDS. Rice et al.[17] suggested that in patients with ARDS, a SpO_2/FiO_2 ratio of 315 corresponded to a PaO_2/FiO_2 ratio of 300. Brown et al.[18] found that the SpO_2/FiO_2 ratio may be reasonably used to substitute arterial blood gas for determining levels of hypoxemia in ARDS patients. Chen et al.[19] further confirmed that patients inferred to have ARDS based on the SpO_2/FiO_2 ratio did not have different clinical outcomes compared to those diagnosed based on the PaO_2/FiO_2 ratio.

As the Berlin definition has been developed with reference to resource-rich settings and does not apply to resource-constrained settings, the Kigali modification of the Berlin definition has been proposed for use in the latter. Following original validation, the Kigali modification, which defines ARDS by the absence of PEEP, a SpO_2/FiO_2 value of ≤315, and bilateral opacities on lung ultrasound or chest radiographs, has been widely used in both clinical practice and research settings.[20] In view of the above-mentioned reasons, a SpO_2/FiO_2 value of ≤315 may be considered instead of a PaO_2/FiO_2 value of ≤300 for the diagnosis of ARDS. Nevertheless, SpO_2 is not linearly associated with PaO_2 and is more easily affected by clinical factors; further evidence is therefore needed to validate this view.

Issue 3: Should the 7-day Period for Acute Onset be Expanded?

Given that nearly all patients with ARDS are identified within 7 days of recognition of the potential risk factors, the Berlin definition specifies a time frame of up to 7 days. Patients with severe COVID-19 always meet other criteria for ARDS except the 7-day period for acute onset.[21] However, the emergence of COVID-19 ARDS (CARDS) has challenged our inherent understanding of ARDS. Berlin et al.[22] reported that hypoxemia caused by COVID-19 generally did not occur within 7 days following the development of initial symptoms, suggesting a slower progression of respiratory failure in COVID-19 than with other causes of ARDS. Zhou et al.[23] found the median time from the onset in CARDS to be 12 days. However, most patients with acute respiratory failure present with newly developing or worsening respiratory symptoms over a period of 7 days.[24] In this context, a previous study on several patients without AIDS found that the time from respiratory symptom onset to the diagnosis of *Pneumocystis jirovecii* pneumonia was >7 days.[25] Another study on patients with H5N1 virus infection found that the median time from the onset of illness to the development of ARDS was 7.5 days.[26] These findings indicate that the timeframe for the diagnosis of ARDS may possibly be extended up to 14 days. However, available data are limited and evidence-based assessment is warranted.

In conclusion, the extension of the Berlin definition is necessary to match the needs of patients, clinicians, and investigators. Modification of the diagnostic criteria for ARDS may allow early identification of patients with less severe diseases and facilitate testing and application of new therapies in those with a high risk of poor outcomes.

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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] Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: Advances in diagnosis and treatment. JAMA 2018;319(7):698–710. doi:10.1001/jama.2017.21907.
[2] 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.
[3] Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372(23):2185–96. doi:10.1056/NEJMoa1503326.
[4] Grieco DL, Menga LS, Cesarano M, Rosà T, Spadaro S, Bitondo MM, et al. Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure: The HENIVOT Randomized Clinical Trial. JAMA 2021;325(17):1731–43. doi:10.1001/jama.2021.4682.
[5] Perkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie JK, et al. Effect of noninvasive respiratory strategies on intubation or mortality among patients with acute hypoxemic respiratory failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial. JAMA 2022;327(6):546–58. doi:10.1001/jama.2022.0028.
[6] Ranieri VM, Tonetti T, Navalesi P, Nava S, Antonelli M, Pesenti A, et al. High-flow nasal oxygen for severe hypoxemia: Oxygenation response and outcome in patients with COVID-19. Am J Respir Crit Care Med 2022;205(4):431–9. doi:10.1164/rccm.202109-2163OC.
[7] Ricard JD, Roca O, Lemiale V, Corley A, Braunlich J, Jones P, et al. Use of nasal high flow oxygen during acute respiratory failure. Intensive Care Med 2020;46(12):2238–47. doi:10.1007/s00134-020-06228-7.
[8] Mauri T, Turrini C, Eronia N, Grasselli G, Volta CA, Bellani G, et al. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. Am J Respir Crit Care Med 2017;195(9):1207–15. doi:10.1164/rccm.201605-0916OC.
[9] Nishimura M. High-flow nasal cannula oxygen therapy in adults: Physiological benefits, indication, clinical benefits, and adverse effects. Respir Care 2016;61(4):529–41. doi:10.4187/respcare.04577.
[10] Delorme M, Bouchard PA, Simon M, Simard S, Lellouche F. Effects of high-flow nasal cannula on the work of breathing in patients recovering from acute respiratory failure. Crit Care Med 2017;45(12):1981–8. doi:10.1097/CCM.0000000000002693.
[11] Kangelaris KN, Ware LB, Wang CY, Janz DR, Zhuo H, Matthay MA, et al. Timing of intubation and clinical outcomes in adults with acute respiratory distress syndrome. Crit Care Med 2016;44(1):120–9. doi:10.1097/CCM.0000000000001359.

[12] García-de-Acilu M, Marin-Corral J, Vázquez A, Ruano L, Magret M, Ferrer R, et al. Hypoxemic patients with bilateral infiltrates treated with high-flow nasal cannula present a similar pattern of biomarkers of inflammation and injury to acute respiratory distress syndrome patients. Crit Care Med 2017;45(11):1845–53. doi:10.1097/CCM.0000000000002647.
[13] Parke RL, Eccleston ML, McGuinness SP. The effects of flow on airway pressure during nasal high-flow oxygen therapy. Respir Care 2011;56(8):1151–5. doi:10.4187/respcare.01106.
[14] Coudroy R, Frat JP, Boissier F, Contou D, Robert R, Thille AW. Early identification of acute respiratory distress syndrome in the absence of positive pressure ventilation: Implications for revision of the berlin criteria for acute respiratory distress syndrome. Crit Care Med 2018;46(4):540–6. doi:10.1097/CCM.0000000000002929.
[15] Matthay MA, Thompson BT, Ware LB. The Berlin definition of acute respiratory distress syndrome: Should patients receiving high-flow nasal oxygen be included? Lancet Respir Med 2021;9(8):933–6. doi:10.1016/S2213-2600(21)00105-3.
[16] Laffey JG, Pham T, Bellani G. Continued under-recognition of acute respiratory distress syndrome after the Berlin definition: What is the solution? Curr Opin Crit Care 2017;23(1):10–17. doi:10.1097/MCC.0000000000000381.
[17] Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB. Comparison of the SpO_2/FiO_2 ratio and the PaO_2/FiO_2 ratio in patients with acute lung injury or ARDS. Chest 2007;132(2):410–17. doi:10.1378/chest.07-0617.
[18] Brown SM, Grissom CK, Moss M, Rice TW, Schoenfeld D, Hou PC, et al. Nonlinear imputation of PaO_2/FiO_2 from SpO_2/FiO_2 among patients with acute respiratory distress syndrome. Chest 2016;150(2):307–13. doi:10.1016/j.chest.2016.01.003.
[19] Chen W, Janz DR, Shaver CM, Bernard GR, Bastarache JA, Ware LB. Clinical characteristics and outcomes are similar in ARDS diagnosed by oxygen saturation/FiO_2 ratio compared with PaO_2/FiO_2 ratio. Chest 2015;148(6):1477–83. doi:10.1378/chest.15-0169.
[20] Riviello Buregeya E, Twagirumugabe T. Diagnosing acute respiratory distress syndrome in resource limited settings: The Kigali modification of the Berlin definition. Curr Opin Crit Care 2017;23(1):18–23. doi:10.1097/MCC.0000000000000372.
[21] Chiumello D, Busana M, Coppola S, Romitti F, Formenti P, Bonifazi M, et al. Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: A matched cohort study. Intensive Care Med 2020;46(12):2187–96. doi:10.1007/s00134-020-06281-2.
[22] Berlin DA, Gulick RM, Martinez FJ. Severe COVID-19. N Engl J Med 2020;383(25):2451–60. doi:10.1056/NEJMcp2009575.
[23] 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.
[24] Azoulay E, Mokart D, Kouatchet A, Demoule A, Lemiale V. Acute respiratory failure in immunocompromised adults. Lancet Respir Med 2019;7(2):173–86. doi:10.1016/S2213-2600(18)30345-X.
[25] Roux A, Canet E, Valade S, Gangneux-Robert F, Hamane S, Lafabrie A, et al. Pneumocystis jirovecii pneumonia in patients with or without AIDS, France. Emerg Infect Dis 2014;20(9):1490–7. doi:10.3201/eid2009.131668.
[26] Yu H, Gao Z, Feng Z, Shu Y, Xiang N, Zhou L, et al. Clinical characteristics of 26 human cases of highly pathogenic avian influenza A (H5N1) virus infection in China. PLoS One 2008;3(8):e2985. doi:10.1371/journal.pone.0002985.