Acute Respiratory Distress Syndrome, Mechanical Ventilation, and Inhalation Injury in Burn Patients

Edward Bittner, MD[a,b], Robert Sheridan, MD[c,*]

KEYWORDS

- ARDS • Burn injury • Inhalation injury • Mechanical ventilation
- Protective ventilation • Ventilator-induced lung injury

KEY POINTS

- Acute respiratory distress syndrome (ARDS) is common in seriously burned patients, driven by a combination of inflammatory and infection factors.
- Inhalation injury contributes to respiratory failure in some burn patients.
- In burn patients, ARDS with or without inhalation injury is effectively managed using principles evolved for non–burn patients.

ACUTE RESPIRATORY DISTRESS SYNDROME

Epidemiology and Pathophysiology

Burn patients are at risk of developing acute respiratory distress syndrome (ARDS) as a result of systemic inflammation, fluid resuscitation, protein loss, prolonged mechanical ventilation (MV), and multiorgan dysfunction (MODS) (**Fig. 1**). Inhalation injury—via direct cellular damage, disruption of mucociliary clearance, airway obstruction, and proinflammatory cytokines—further increases the risk.[1] Between 20% and 50% of mechanically ventilated burn patients will develop ARDS. Onset is most commonly during the first week postburn, although it may be delayed.[2,3] Pathologically, ARDS is acutely characterized by inflammation-mediated injury resulting in increased alveolar-capillary permeability, edema, alveolar collapse/derecruitment, reduced lung compliance, increased pulmonary vascular resistance, ventilation-perfusion (VQ) mismatch and shunting, and impaired gas exchange.[4] Chronic changes are

[a] Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital and Shriners Hospital for Children, 51 Blossom Street, Boston, MA 02114, USA; [b] Department of Anesthesia, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA; [c] Department of Surgery, Massachusetts General Hospital and Shriners Hospital for Children, 51 Blossom Street, Boston, MA 02114, USA
* Corresponding author.
E-mail address: rsheridan@mgh.harvard.edu

Surg Clin N Am 103 (2023) 439–451
https://doi.org/10.1016/j.suc.2023.01.006 surgical.theclinics.com

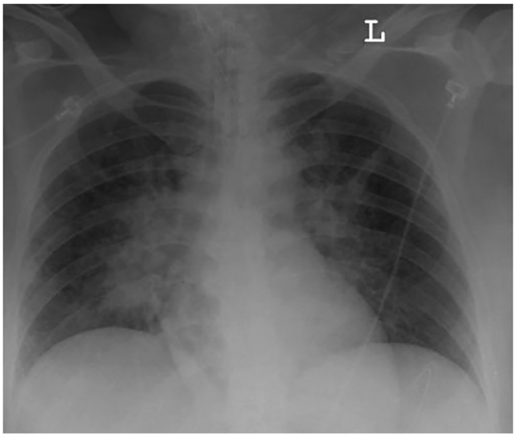

Fig. 1. Postburn ARDS are often nonspecific, showing inhomogeneous consolidation and perihilar fullness.

characterized by fibrosis, vascular smooth muscle hypertrophy, and capillary obliteration.[4] ARDS contributes to mortality and morbidity in burn patients.[5] Mortality in ARDS is caused primarily by the development of MODS.[6]

The management of ARDS is largely supportive, and most approaches in burn patients have been translated from the non–burn population. Although MV is often essential, the process itself can inflict further damage to the lungs, referred to as ventilator-induced lung injury (VILI).[7] Mechanisms of VILI include high inspiratory pressures (barotrauma), high tidal volumes (TV; volutrauma), repeated opening and closing of alveoli (atelectrauma), oxygen toxicity, and inflammatory cytokine release (biotrauma).[8,9] Recently, additional mechanisms of injury have been implicated, including high mechanical power (ergotrauma), stress frequency, respiratory muscle overuse/underuse (myotrauma), and pulmonary capillary stress failure.[10–12]

Protective Ventilation

The standard approach to protective mechanical ventilation (PMV) includes small TVs to limit volutrauma, setting positive end-expiratory pressure (PEEP) to minimize atelectrauma, and recruitment maneuvers (RMs) to open collapsed regions of the lung. An individualized approach to MV based on lung pathophysiology and morphology, ARDS cause, and lung imaging and monitoring has been suggested to improve ventilation practice and outcome.[13] In addition, PMV has been expanded beyond the lung itself to include right-heart-protective ventilation, diaphragmatic-protective ventilation, minimization of repetitive-stress injury, capillary-stress reduction, and consideration of patient self-inflicted lung injury (P-SILI).[11]

Tidal Volumes

A TV of 4 to 6 mL/kg predicted body weight is commonly used to maintain a plateau pressure (Pplat) < 30 cm H_2O.[14] Minimizing airway driving pressure (DP), calculated as Pplat minus PEEP, is another suggested strategy for selecting TV.[15] Importantly, Pplat and DP are indirect measures for peak lung stress. When functional residual capacity is markedly reduced in severe ARDS, overdistention can occur in nondependent regions despite achieving target levels. Real-time bedside monitoring with pressure and imaging techniques, such as esophageal manometry, electrical impedance tomography, and lung ultrasound, are increasingly used to select TV to minimize overdistention.[16–18]

Unique characteristics of burn patients may affect the successful application of a low-TV approach. For example, low TV in a burn patient with poor chest compliance and/or inhalation injury with obstruction of the conducting airways can result in lung underinflation. A retrospective study in pediatric burn patients with inhalation injury found that a low-TV approach was associated with more atelectasis, longer duration of MV, and a higher incidence of ARDS than a higher-TV approach.[19] A recent international cohort study found that low-TV ventilation was used in most burn patients, but was not associated with a reduction in days ventilator-free and alive at day 28.[20] Strict application of low-TV ventilation in the setting of increased CO_2 production from burn-associated hypermetabolism can result in “air hunger,” patient-ventilator dyssynchrony, and hypercapnia. Although hypercapnia may be tolerated to an extent (“permissive hypercapnia”), adjustments to the ventilator mode and increases in sedation are often needed.

POSITIVE END-EXPIRATORY PRESSURE

PEEP is used in ARDS to minimize atelectasis and reduce lung heterogeneity, thereby increasing the amount of aerated lung available for ventilation. PEEP may also shift edema fluid from the flooded alveoli into the interstitial space, decreasing shunt fraction and promoting more uniform alveolar mechanics.[8] However, PEEP will only have benefit when alveolar recruitment surpasses overexpansion of patent alveoli. There is no simple method to assess the risk-to-benefit ratio of different PEEP levels. In ARDS, derecruitment is a continuous process in which the rate of collapse increases as PEEP decreases. With decreasing levels of PEEP, derecruitment ceases in the sternal lung zones at PEEP of 10 cm H_2O, whereas it continues in dorsal regions down to 0 cm H_2O.[21] Consequently, a minimum PEEP of 10 to 12 cm H_2O might reduce derecruitment during the acute phase of ARDS, and higher levels may be necessary in severe cases. Approaches to select an optimal PEEP level in ARDS include the use of tables that assign PEEP based on FiO_2, use of the highest PEEP that optimizes oxygenation while allowing an acceptable TV and Pplat, and bedside PEEP titration based on lung compliance and recruitability.[22]

Recruitment Maneuvers

Computed tomographic (CT) scans have indicated that tissue consolidation can account for up to 50% of the lung in ARDS.[23] RMs apply a higher-than-normal inflation pressure (usually $\geq$35 cm H_2O) to the lungs for 20 to 40 seconds to “open the lung” by recruiting atelectatic regions.[24] Evidence to support their routine use in ARDS is lacking.[25] However, RMs may be beneficial for improving oxygenation in patients with hypoxemia.[25] The improvement in oxygenation from an RM is often greatest when followed by an increase in the level of PEEP.[25] Repeated RMs during lung-protective ventilation can improve pulmonary compliance and oxygenation and do not appear to worsen lung injury in severe ARDS.[26] Most alveolar recruitment occurs during the first 10 seconds of an RM; extended durations (eg, minutes) may be associated with worse outcomes.[27] RMs appear to be most effective in improving oxygenation during early ARDS rather than during the fibroproliferative phase.[28]

Right-Heart-Protective Ventilation

Pulmonary hypertension (PH) in ARDS results from pulmonary vasoconstriction (caused by hypoxia or hypercarbia), microthrombosis, and ventilation with high

DPs.[29] Right-ventricular (RV) dysfunction develops with sustained elevations in PH, as the RV has no adaptive mechanism other than dilatation when its afterload is increased.[30] In ARDS, RV dysfunction can lead to RV failure (acute cor pulmonale), and if left untreated, cardiogenic shock can develop. Elevated right-heart pressure can also worsen hypoxemia by right-to-left intracardiac shunting of deoxygenated blood through a patent foramen ovale. RV PMV has been suggested to reduce RV afterload to include the following: (1) minimizing lung stress by limiting Pplat and DP, (2) reducing pulmonary vasoconstriction by improving oxygenation and control of CO_2, and (3) prone positioning (PP) to unload the RV.[31] Optimization of RV-protective PEEP must balance alveolar recruitment and overdistention. If RV-protective measures are insufficient (or unfeasible), ancillary therapies, such as inhaled vasodilators or extracorporeal membrane oxygenation (ECMO), may be required.

Diaphragm

Respiratory-muscle weakness rapidly develops in critically ill, mechanically ventilated patients and carries a poorer prognosis.[32,33] Exposure to excessive workloads even for brief periods can result in diaphragmatic inflammation referred to as use atrophy.[11] Failing to allow full rest following the onset of acute respiratory failure or after a failed weaning trial can induce this injury and prolong MV.[11] Furthermore, sepsis can incite and exacerbate diaphragmatic injury, through the effects of proinflammatory cytokines.[34] Disuse atrophy can result from prolonged periods of MV and loss of electromyographic stimulation.[35] Diaphragmatic PMV uses the following dual approach[12]: (1) early after the onset of acute respiratory failure, avoiding prolonged periods of high work of breathing (WOB) by providing adequate ventilatory support and sedation; (2) during recovery, limiting passive ventilation and targeting an inspiratory effort level similar to that of healthy subjects at rest to accelerate liberation from ventilation.[33]

Self-Induced Lung Injury

Increased respiratory drive and vigorous inspiratory efforts are often attempts to compensate for impairments in respiratory mechanics and gas exchange. These vigorous spontaneous breathing efforts may have injurious physiologic effects mediated by swings in transpulmonary pressure (TPP), increases in transvascular pressure resulting in edema, intratidal shift of gas between different lung zones (pendelluft), and diaphragmatic injury. This is referred to as P-SILI.[36] In patients receiving MV, vigorous respiratory efforts may also result in patient-ventilator dyssynchrony and increased mechanical lung injury owing to high TPPs and/or cyclic atelectasis.[37,38] Preventing P-SILI in clinical practice requires assessment of a patient's inspiratory effort and the detection of potentially harmful patient-ventilator interactions. For some patients with vigorous spontaneous breathing and/or patient-ventilator dyssynchrony, sedation or paralysis may be protective treatment.

Stress Frequency and Permissive Hypercapnia

Higher ventilatory frequencies are often used with low-TV ventilation to reduce hypercapnia, but this may have detrimental effects on respiratory mechanics, gas exchange, and cumulative lung trauma.[39,40] Higher ventilatory frequencies shorten inspiratory time, resulting in the need for higher peak-flow rates, which may augment parenchymal shear stress, worsen oxygenation, and contribute to greater pressure-related cyclic lung stress and strain. Shortened expiration times may have detrimental effects, including dynamic hyperinflation, reduced compliance, increased TPP, and diaphragmatic dysfunction. A reduction of the frequency of ventilation with resulting hypercapnia may be beneficial in ARDS by facilitating a reduction of the cumulative intensity of cyclic stress and strain. Hypercapnia itself may also have beneficial physiologic benefits, including improved VQ matching from pulmonary vasoconstriction, increased local alveolar ventilation from inhibition of airway tone, increased oxygen delivery from an increase in cardiac output, increased unloading of oxygen in the tissues, microvascular vasodilation, and anti-inflammatory effects.[41] Some studies have reported benefit from permissive hypercapnia in ARDS, although they are confounded by the inability to dissect the effects of permissive hypercapnia from the effects of low TV.[42] Because hypercapnia increases respiratory drive, deep sedation or neuromuscular blockade may be required.

Fluid Overload and Capillary Stress Reduction

Fluid-conservative approaches have been associated with improved outcomes in non–burn ARDS, but have the potential to compromise burn resuscitation.[43] Consequently, application of a fluid-conservative approach in a burn patient with ARDS should be considered carefully, with close attention to administering the least amount of fluid that still achieves adequate organ perfusion.

Unconventional Mechanical Ventilation

A variety of unconventional modes of MV, including high-frequency percussive ventilation (HFPV), high-frequency oscillatory ventilation (HFOV), or airway-pressure-release ventilation (APRV), are used in some burn centers for patients with ARDS.[44]

HFPV delivers very small, high-frequency tidal breaths superimposed on a conventional pressure-controlled breath.[45] HFPV improves oxygenation, improves ventilation, and lowers airway pressures compared with other modes of MV. HFPV also produces intrabronchial percussion, airway turbulence, and higher airflow, all of which enhance mobilization and clearance of airway debris and secretions. HFPV, although shown not to be superior to conventional ventilation in the general ARDS population, has a suggested role in inhalation injuries and burn-related ARDS.[46] HFPV is routinely used in some burn centers, particularly in patients with inhalation injury or in those who fail conventional MV.

HFOV delivers small, sub-dead-space TVs at high frequency to maximize lung recruitment and avoid cyclic alveolar collapse.[47] HFOV in burn-related ARDS has not been extensively studied. HFOV is sometimes used as a rescue approach for burn patients with refractory hypoxemia but is generally unsuccessful in improving oxygenation in inhalation injury, probably because effective lung recruitment is impaired by obstruction of the conducting airways.[48]

APRV is a mode of pressure-controlled ventilation that allows spontaneous breathing at regularly fluctuating high and low levels of continuous positive airway pressure.[49] Proposed benefits include alveolar recruitment and stabilization, improved VQ matching, increased mean airway pressure, and minimization peak and Pplats.[50] Spontaneous breathing in APRV reduces sedation requirements, thereby preserving airway reflexes and facilitating cough and pulmonary toilet. There is limited literature supporting the benefit of APRV for ARDS. Specific evidence in the burn population is lacking.

Noninvasive Ventilation

For patients with mild ARDS, noninvasive ventilation (NIV) may be beneficial, as it allows patients to communicate more easily, requires less sedation, allows more effective cough and expectoration of secretions, and avoids intubation-related complications. NIV appears safe and effective in mild to moderate hypoxemia, but it may delay intubation and increase mortality in more severe hypoxemia.[51] In patients with inhalation injury or that have received large-volume fluid resuscitation, NIV may mask evidence of progressive airway obstruction.[52] There is currently limited literature examining the impact of NIV in the burn population.[53]

High-Flow Nasal Cannula

High-flow nasal cannula (HFNC) is increasingly used in the management of respiratory failure, including mild ARDS.[54] HFNC is capable of delivering up to 100% heated and humidified oxygen at flow rates of up to 60 L per minute. The benefits include a reduction in WOB, reduction of the anatomic dead space, generation of a small amount of PEEP, and improvement of mucociliary clearance.[55] There are limited reports of HFNC use in patients with burns and/or inhalation injury.[56]

STRATEGIES FOR REFRACTORY HYPOXEMIA

Prone Positioning

When a patient with ARDS is turned from supine to prone, the atelectatic dorsal lung regions are freed from the weight of the more ventral lung, the heart, and the mediastinum, favoring expansion of dorsal regions. The net effect is more homogeneous aeration with a more uniform strain distribution leading to an improvement of gas exchange and a decreased risk of VILI.[57] A systematic review of 9 randomized controlled trials (RCTs) concluded that patients with ARDS most likely to derive a survival benefit from PP were those with severe hypoxemia and in whom it was used more than 16 hours per day.[58] Data on PP of burn patients are limited; it presents logistical and safety challenges.[59] A case series reports improvements in oxygenation and a low rate of complications in patients with burn-related ARDS undergoing PP.[60] PMV should continue to be used during PP, and reassessment of ventilatory parameters should be performed, as respiratory mechanics may change with proning.[61,62] Increased sedation and neuromuscular blockade may be required.

Neuromuscular Blockade

Neuromuscular blocking agents (NMBAs) are sometimes used in patients with severe ARDS to enhance gas exchange and reduce Pplats, ventilator dyssynchrony, and VILI. A meta-analysis of 5 RCTs in moderate to severe ARDS concluded that early initiation (within 36–48 hours of ARDS diagnosis) of a 48-hour infusion of cisatracurium improved oxygenation and lowered barotrauma risk without increasing intensive care unit weakness.[63] There is no specific evidence to guide the use of NMBAs in burn-injured patients with ARDS. It is reasonable to consider them in burn patients with severe ARDS.[64]

Inhaled Pulmonary Vasodilators

Inhaled pulmonary vasodilators, including nitric oxide (NO) and epoprostenol, selectively increase blood flow to ventilated lung regions, thereby improving VQ matching and improving oxygenation.[65] They can also benefit ARDS patients with right-heart failure. A meta-analysis of 14 RCTs in adults with ARDS found that inhaled NO increased oxygenation but did not affect duration of MV or survival.[66] Improvement in oxygenation with inhaled NO has been demonstrated in burn-injured patients with ARDS.[67] Inhaled epoprostenol is a less-expensive agent that has similar effects.[68]

Extracorporeal Life Support

If other rescue strategies used in ARDS management fail to improve oxygenation, ECMO may be beneficial. A recent report concluded that mortality for burn-injured patients receiving ECMO was comparable that for non–burn ECMO patients.[69] Considerations include the risks of anticoagulation, need for further operative care, and consideration of the goals or futility of care.[70] Patients most likely to benefit from ECMO are those with severe ARDS within the first week of MV and without multiple organ failure.[71] ECMO for burn patients should be provided only in centers experienced in both burn care and in the use of extracorporeal support for ARDS.

INHALATION INJURY

Usually sustained in structural or vehicular fires, inhalation injury occurs in about 5% of burn-unit admissions.[72,73] Survival has improved with the evolution of supportive respiratory care, but inhalation injury remains a significant source of morbidity and mortality in burn patients. It increases mortality in patients with large cutaneous burns.[74]

Pathophysiology

The smoke generated during structural fires contains many incomplete combustion products, chemicals, and fine debris with varied particle size and weight. Gas temperatures can rise above floor level to several hundred degrees Fahrenheit. Exposure to such temperatures in inhaled gas can cause direct thermal damage to the supraglottic airway. Rarely, particularly with steam inhalation injury in enclosed spaces, thermal injury below the glottis can occur. Aerosolized irritants can cause inflammation, bronchospasm, increased bronchial blood flow, surfactant depletion, and mucosal slough. The local response to inhaled irritants attracts inflammatory cells, generates reactive oxygen species, and causes local release of proinflammatory molecules.[75] These can induce variable degrees of alveolar flooding and bronchial exudate with secondary VQ mismatching. These inflammatory changes are thought to explain the significant resuscitation fluid volume required by burn patients with inhalation injury.[76–78] Inhalation injury may be accompanied and complicated by carbon monoxide and/or cyanide poisoning.

Inhalation injury carries a strong risk of ARDS, and of pneumonia secondary to sloughing of the respiratory epithelium with resulting loss of ciliary clearance and accrual of obstructive endobronchial debris. This results in small-airway occlusion, atelectasis, and infection. Deaths owing to inhalation injury are often related to secondary ARDS and infection, with a classic report suggesting up to a 60% increase in expected burn mortality in the setting of coincident inhalation injury and pneumonia.[79]

Diagnosis

Tools to evaluate the presence and severity of inhalation injury include clinical evaluation, bronchoscopy, and radiography. Unfortunately, none of these tools reliably predict clinical course.[80] Severity grading schemes have been proposed,[81] but have not proven to be reliably useful for clinical care. History and clinical presentation are the most reliable methods of evaluation. Burns occurring in a closed space, burns around the nose and mouth, singed nasal hair, soot in the airway, carbonaceous sputum, hoarseness, wheezing, and stridor all suggest inhalation injury. Bronchoscopic examination will often reveal carbonaceous debris, ulceration, pallor, and mucosal slough, although patients inhaling fine-particle smoke or burning hydrocarbons may have deceptively unremarkable bronchoscopy. Those with overt bronchoscopic signs on initial evaluation seem to have more challenging clinical courses.[82] Serial bronchoscopy for pulmonary toilet may have value later in the hospital course, but there is no demonstrated role for early bronchoscopic removal of visible soot. Early chest radiographs are usually normal. Radionuclide ventilation scanning with xenon-133, technetium-99 DTPA, or macroaggregated albumin may show inhomogeneous tracer clearance suggestive of small airway obstruction.[83] CT scanning has been proposed for early diagnosis.[84–88]

Management

During initial evaluation, intubation is indicated for usual reasons of obtunded mental state or respiratory distress. Inhalation injury alone does not mandate intubation unless airway patency is threatened, particularly if cutaneous burns are small. In patients with severe facial edema or stridor, rapid assessment is critical, and intubation is often required. Evolving upper airway edema may complicate reintubation, so tube security is essential. Routine use of prophylactic antibiotics or empiric steroids is not supported.

Inhalation injury is associated with mucosal slough and loss of ciliary clearance with compromised pulmonary toilet. Chest physiotherapy and suctioning or stimulated cough is front-line therapy. Uncommonly, repeated bronchoscopy for pulmonary toilet may be needed.[89] Tracheobronchitis and pneumonia may occur and are addressed with targeted antibiotics and pulmonary toilet. Additional proposed therapies have included HFPV,[90] high-volume ventilation,[91] and nebulized heparin and N-acetylcysteine.[92] Tracheostomy, weaning, and extubation follow standard critical-care indications. Rarely, patients will suffer tracheal injury requiring reconstruction[93]; most survivors have no long-term pulmonary sequalae.[94]

SUMMARY

ARDS is common in patients with burn injury, and the need for large-volume fluid resuscitation, frequent surgery, presence of inhalation injury, superimposed sepsis, and burn-associated hypermetabolism all contribute to ventilation challenges.

CLINICS CARE POINTS

- Respiratory distress and failure are common occurences in burn patients driven by direct respiratory system injury, pulmonary and systemic infection, and systemic inflammation
- Inhalalation injury is caused by inhaled irritants and can result in multi-level iinvolvement of the respiratory system

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Lam NN, Hung TD. ARDS among cutaneous burn patients combined with inhalation injury: early onset and bad outcome. Ann Burns Fire Disasters 2019;32: 37–42.
2. Lam NN, Hung TD, Hung DK. Acute respiratory distress syndrome among severe burn patients in a developing country: application result of the berlin definition. Ann Burns Fire Disasters 2018;31:9–12.
3. Cartotto R, Li Z, Hanna S, et al. The acute respiratory distress syndrome (ARDS) in mechanically ventilated burn patients: an analysis of risk factors, clinical features, and outcomes using the Berlin ARDS definition. Burns 2016;42:1423–43.

4. Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. Nat Rev Dis Primers 2019;5:18.
5. Zavlin D, Chegireddy V, Boukovalas S, et al. Multi-institutional analysis of independent predictors for burn mortality in the United States. Burns Trauma 2018;6:24.
6. Del Sorbo L, Slutsky AS. Acute respiratory distress syndrome and multiple organ failure. Curr Opin Crit Care 2011;17:1–6.
7. Beitler JR, Malhotra A, Thompson BT. Ventilator-induced Lung Injury. Clin Chest Med 2016;37:633–46.
8. Ohshimo S. Oxygen administration for patients with ARDS. J Intensive Care 2021;9:17.
9. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med 2013;369:2126–36.
10. Kallet RH. Mechanical Ventilation in ARDS: Quo Vadis? Respir Care 2022;67:730–49.
11. Marini JJ. Evolving concepts for safer ventilation. Crit Care 2019;23:114.
12. Bertoni M, Spadaro S, Goligher EC. Monitoring patient respiratory effort during mechanical ventilation: lung and diaphragm-protective ventilation. Crit Care 2020;24:106.
13. Pelosi P, Ball L, Barbas CSV, et al. Personalized mechanical ventilation in acute respiratory distress syndrome. Crit Care 2021;25:250.
14. Papazian L, Aubron C, Brochard L, et al. Formal guidelines: management of acute respiratory distress syndrome. Ann Intensive Care 2019;9:69.
15. Pereira Romano ML, Maia IS, Laranjeira LN, et al. Driving Pressure-limited Strategy for Patients with Acute Respiratory Distress Syndrome. A Pilot Randomized Clinical Trial. Ann Am Thorac Soc 2020;17:596–604.
16. Pham T, Telias I, Beitler JR. Esophageal Manometry. Respir Care 2020;65:772–92.
17. Rubin J, Berra L. Electrical impedance tomography in the adult intensive care unit: clinical applications and future directions. Curr Opin Crit Care 2022;28:292–301.
18. Cylwik J, Buda N. Lung Ultrasonography in the Monitoring of Intraoperative Recruitment Maneuvers. Diagnostics 2021;11:276.
19. Sousse LE, Herndon DN, Andersen CR, et al. High tidal volume decreases adult respiratory distress syndrome, atelectasis, and ventilator days compared with low tidal volume in pediatric burned patients with inhalation injury. J Am Coll Surg 2015;220:570–8.
20. Schultz MJ, Horn J, Hollmann MW, et al. LAMiNAR investigators. Ventilation practices in burn patients-an international prospective observational cohort study. Burns Trauma 2021;9. tkab034.
21. Crotti S, Mascheroni D, Caironi P, et al. Recruitment and derecruitment during acute respiratory failure: a clinical study. Am J Resp Crit Care Med 2001 Jul 1;164(1):131–40.
22. Gattinoni L, Collino F, Maiolo G, et al. Positive end-expiratory pressure: how to set it at the individual level. Ann Transl Med 2017;5:288.
23. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006;354:1775–86.
24. Hess DR. Recruitment Maneuvers and PEEP Titration. Respir Care 2015;60:1688–704.
25. Pensier J, de Jong A, Hajjej Z, et al. Effect of lung recruitment maneuver on oxygenation, physiological parameters and mortality in acute respiratory distress

syndrome patients: a systematic review and meta-analysis. Intensive Care Med 2019;45:1691–702.
26. Li MQ, Han GJ, Li JQ, et al. Effect of Repeated Recruitment Manoeuvres on Patients with Severe Acute Respiratory Distress Syndrome. West Indian Med J 2015;64:362–6.
27. Arnal JM, Paquet J, Wysocki M, et al. Optimal duration of a sustained inflation recruitment maneuver in ARDS patients. Intensive Care Med 2011;37:1588–94.
28. Spieth PM, Gama de Abreu M. Lung recruitment in ARDS: we are still confused, but on a higher PEEP level. Crit Care 2012;16:108.
29. Revercomb L, Hanmandlu A, Wareing N, et al. Mechanisms of Pulmonary Hypertension in Acute Respiratory Distress Syndrome (ARDS). Front Mol Biosci 2021 Jan 18;7:624093.
30. Zochios V, Parhar K, Tunnicliffe W, et al. The Right Ventricle in ARDS. Chest 2017;152:181–93.
31. Paternot A, Repesse X, Vieillard-Baron A. Rationale and description of right ventricle-protective ventilation in ARDS. Respir Care 2016;61:1391–6.
32. Jaber S, Petrof BJ, Jung B, et al. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. Am J Respir Crit Care Med 2011;183:364–71.
33. Goligher EC, Dres M, Fan E, et al. Mechanical Ventilation-induced Diaphragm Atrophy Strongly Impacts Clinical Outcomes. Am J Respir Crit Care Med 2018;197:204–13.
34. Hussain SN, Simkus G, Roussos C. Respiratory muscle fatigue: a cause of ventilatory failure in septic shock. J Appl Physiol 1985;58:2033–40.
35. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 2008;358:1327–35.
36. Carteaux G, Parfait M, Combet M, et al. Patient-Self Inflicted Lung Injury: A Practical Review. J Clin Med 2021;10:2738.
37. Yoshida T, Uchiyama A, Matsuura N, et al. Spontaneous breathing during lung-protective ventilation in an experimental acute lung injury model: high transpulmonary pressure associated with strong spontaneous breathing effort may worsen lung injury. Crit Care Med 2012;40:1578–85.
38. Yoshida T, Torsani V, Gomes S, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. Am J Respir Crit Care Med 2013;188:1420–7.
39. Tonetti T, Vasques F, Rapetti F, et al. Driving pressure and mechanical power: new targets for VILI prevention. Ann Transl Med 2017;5:286.
40. Akoumianaki E, Vaporidi K, Georgopoulos D. The Injurious Effects of Elevated or Nonelevated Respiratory Rate during Mechanical Ventilation. Am J Respir Crit Care Med 2019;199:149–57.
41. Curley GF, Laffey JG, Kavanagh BP. CrossTalk proposal: there is added benefit to providing permissive hypercapnia in the treatment of ARDS. J Physiol 2013;591:2763–5.
42. Barnes T, Zochios V, Parhar K. Re-examining Permissive Hypercapnia in ARDS: A Narrative Review. Chest 2018 Jul;154(1):185–95.
43. Guilabert P, Usúa G, Martín N, et al. Fluid resuscitation management in patients with burns: update. Br J Anaesth 2016;117:284–96.
44. Folwell JS, Basel AP, Britton GW, et al. Mechanical Ventilation Strategies in the Critically Ill Burn Patient: A Practical Review for Clinicians. Eur. Burn J 2021;2:140–51.
45. Miller AG, Bartle RM, Feldman A, et al. A narrative review of advanced ventilator modes in the pediatric intensive care unit. Transl Pediatr 2021;10:2700–19.

46. Chung KK, Rhie RY, Lundy JB, et al. A Survey of Mechanical Ventilator Practices Across Burn Centers in North America. J Burn Care Res 2016;37:e131–9.
47. Sklar MC, Fan E, Goligher EC. High-Frequency Oscillatory Ventilation in Adults With ARDS: Past, Present, and Future. Chest 2017;152:1306–17.
48. Cartotto R, Walia G, Ellis S, et al. Oscillation after inhalation: high frequency oscillatory ventilation in burn patients with the acute respiratory distress syndrome and co-existing smoke inhalation injury. J Burn Care Res 2009;30:119–27.
49. Swindin J, Sampson C, Howatson A. Airway pressure release ventilation. BJA Educ 2020;20:80–8.
50. Fredericks AS, Bunker MP, Gliga LA, et al. Airway Pressure Release Ventilation: A Review of the Evidence, Theoretical Benefits, and Alternative Titration Strategies. Clin Med Insights Circ Respir Pulm Med 2020;14:1179548420903297.
51. Non-invasive ventilatory support and high-flow nasal oxygen as first-line treatment of acute hypoxemic respiratory failure and ARDS. Intensive Care Med 2021;47:851–66.
52. Goh CT, Jacobe S. Ventilation strategies in paediatric inhalation injury. Paediatr Respir Rev 2016;20:3–9.
53. Endorf FW, Dries DJ. Noninvasive ventilation in the burned patient. J Burn Care Res 2010;31:217–28.
54. Helviz Y, Einav S. A Systematic Review of the High-flow Nasal Cannula for Adult Patients. Crit Care 2018;22:71.
55. Nishimura M. High-flow nasal cannula oxygen therapy in adults. J Intensive Care 2015;3:15.
56. Byerly FL, Haithcock JA, Buchanan IB, et al. Use of high flow nasal cannula on a pediatric burn patient with inhalation injury and post-extubation stridor. Burns 2006;32:121–5.
57. Guérin C, Albert RK, Beitler J, et al. Prone position in ARDS patients: why, when, how and for whom. Intensive Care Med 2020;46:2385–96.
58. Bloomfield R, Noble DW, Sudlow A. Prone position for acute respiratory failure in adults. Cochrane Database Syst Rev 2015;11:CD008095.
59. Oto B, Orosco RI, Panter E, et al. Prone Positioning of the Burn Patient With Acute Respiratory Distress Syndrome: A Review of the Evidence and Practical Considerations. J Burn Care Res 2018;39:471–5.
60. Hale DF, Cannon JW, Batchinsky AI, et al. Prone positioning improves oxygenation in adult burn patients with severe acute respiratory distress syndrome. J Trauma Acute Care Surg 2012;72:1634–9.
61. Park SY, Kim HJ, Yoo KH, et al. The efficacy and safety of prone positioning in adults patients with acute respiratory distress syndrome: a meta-analysis of randomized controlled trials. J Thorac Dis 2015;7:356–67.
62. Papazian L, Munshi L, Guérin C. Prone position in mechanically ventilated patients. Intensive Care Med 2022;48:1062–5.
63. Ho ATN, Patolia S, Guervilly C. Neuromuscular blockade in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. J Intensive Care 2020;8:12.
64. Martyn JAJ, Sparling JL, Bittner EA. Molecular mechanisms of muscular and non-muscular actions of neuromuscular blocking agents in critical illness. Br J Anaesth 2022;S0007-0912(22):00451–2.
65. Torbic H, Szumita PM, Anger KE, et al. Inhaled epoprostenol vs inhaled nitric oxide for refractory hypoxemia in critically ill patients. J Crit Care 2013;28:844–8.

66. Gebistorf F, Karam O, Wetterslev J, et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev 2016;2016:CD002787.
67. Sheridan RL, Hurford WE, Kacmarek RM, et al. Inhaled nitric oxide in burn patients with respiratory failure. J Trauma 1997;42:629–34.
68. Fuller BM, Mohr NM, Skrupky L, et al. The use of inhaled prostaglandins in patients with ARDS: a systematic review and meta-analysis. Chest 2015;147:1510–22.
69. Nosanov LB, McLawhorn MM, Vigiola Cruz M, et al. A National Perspective on ECMO Utilization in Patients with Burn Injury. J Burn Care Res 2017;39:10–4.
70. Kennedy JD, Thayer W, Beuno R, et al. ECMO in major burn patients: feasibility and considerations when multiple modes of mechanical ventilation fail. Burns Trauma 2017;5:20.
71. Combes A, Peek GJ, Hajage D, et al. ECMO for severe ARDS: systematic review and individual patient data meta-analysis. Intensive Care Med 2020;46:2048–57.
72. Veeravagu A, Yoon BC, Jiang B, et al. National trends in burn and inhalation injury in burn patients: results of analysis of the nationwide inpatient sample database. J Burn Care Res 2015;36(2):258–65.
73. Aub JC, Pittman H, Brues AM. The pulmonary complications: a clinical description. Ann Surg 1943 Jun;117(6):834–40.
74. Ryan C, Schoenfeld R, Thorpe W, et al. Objective estimates of the probability of death from burn injuries. NEJM 1998;338:362–6.
75. Albright JM, Davis CS, Bird MD, et al. The acute pulmonary inflammatory response to the graded severity of smoke inhalation injury. Crit Care Med 2012 Apr;40(4):1113–21.
76. Endorf FW, Gamelli RL. Inhalation injury, pulmonary perturbations, and fluid resuscitation. J Burn Care Res 2007 Jan-Feb;28(1):80–3.
77. Barillo DJ, Goode R, Esch V. Cyanide poisoning in victims of fire: analysis of 364 cases and review of the literature. J Burn Care Rehabil 1994;15(1):46–57.
78. Cumpston KL, Rodriguez V, Nguyen T, et al. Evaluation of prehospital hydroxocobalamin use in the setting of smoke inhalation. Am J Emerg Med 2021 Dec;50:365–8.
79. Shirani KZ, Pruitt BA Jr, Mason AD Jr. The influence of inhalation injury and pneumonia on burn mortality. Ann Surg 1987 Jan;205(1):82–7.
80. Hassan Z, Wong JK, Bush J, et al. Assessing the severity of inhalation injuries in adults. Burns 2010 Mar;36(2):212–6.
81. Ryan CM, Fagan SP, Goverman J, et al. Grading inhalation injury by admission bronchoscopy. Crit Care Med 2012 Apr;40(4):1345–6.
82. Spano S, Hanna S, Li Z, et al. Does Bronchoscopic Evaluation of Inhalation Injury Severity Predict Outcome? J Burn Care Res 2016;37(1):1–11.
83. Shiau YC, Liu FY, Tsai JJ, et al. Usefulness of technetium-99m hexamethylpropylene amine oxime lung scan to detect inhalation lung injury of patients with pulmonary symptoms/signs but negative chest radiograph and pulmonary function test findings after a fire accident–a preliminary report. Ann Nucl Med 2003;17(6):435–8.
84. Yamamura H, Morioka T, Hagawa N, et al. Computed tomographic assessment of airflow obstruction in smoke inhalation injury: Relationship with the development of pneumonia and injury severity. Burns 2015;41(7):1428–34.
85. Roderique JD, Josef CS, Feldman MJ, et al. A modern literature review of carbon monoxide poisoning theories, therapies, and potential targets for therapy advancement. Toxicology 2015;334:45–58.

86. Buckley NA, Juurlink DN, Isbister G, et al. Hyperbaric oxygen for carbon monoxide poisoning. Cochrane Database Syst Rev 2011;4:CD002041.
87. Dumestre D, Nickerson D. Use of cyanide antidotes in burn patients with suspected inhalation injuries in North America: a cross-sectional survey. J Burn Care Res 2014;35(2):e112–7.
88. Anseeuw K, Delvau N, Burillo-Putze G, et al. Cyanide poisoning by fire smoke inhalation: a European expert consensus. Eur J Emerg Med 2013;20(1):2–9.
89. Carr JA, Crowley N. Prophylactic sequential bronchoscopy after inhalation injury: results from a three-year prospective randomized trial. Eur J Trauma Emerg Surg 2013;39(2):177–83.
90. Ashry HS, Mansour G, Kalil AC, et al. Incidence of ventilator associated pneumonia in burn patients with inhalation injury treated with high frequency percussive ventilation versus volume control ventilation: A systematic review. Burns 2016;S0305–4179.
91. Sousse LE, Herndon DN, Andersen CR, et al. High tidal volume decreases adult respiratory distress syndrome, atelectasis, and ventilator days compared with low tidal volume in pediatric burned patients with inhalation injury. J Am Coll Surg 2015;220(4):570–8.
92. Miller AC, Elamin EM, Suffredini AF. Inhaled anticoagulation regimens for the treatment of smoke inhalation-associated acute lung injury: a systematic review. Crit Care Med 2014;42(2):413–9.
93. Gaissert HA, Lofgren RH, Grillo HC. Upper airway compromise after inhalation. Complex strictures of the larynx and trachea and their management. Ann Surg 1993;218(5):672–8.
94. Palmieri TL. Long term outcomes after inhalation injury. J Burn Care Res 2009;30(1):201–3.