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REVIEW ARTICLE

Perioperative ARDS and lung injury: for anaesthesia and beyond

Robert Wise[a]*, David Bishop[a], Gavin Joynt[b] and Reitze Rodseth[ac]

[a]*Perioperative Research Unit, Metropolitan Department of Anaesthetics, Critical Care and Pain Management, Pietermaritzburg, University of KwaZulu-Natal, Discipline of Anaesthesiology and Critical Care, Durban, South Africa*
[b]*Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Shatin, Hong Kong*
[c]*Outcomes Research Consortium, Cleveland Clinic, Cleveland, OH, USA*
**Corresponding author, email: Robert.Wise@kznhealth.gov.za*

Postoperative pulmonary complications are common and may be associated with significant cost. Acute respiratory distress syndrome (ARDS), a life-threatening respiratory disease process characterised by hypoxaemia and reduced lung compliance, is one of the more serious pulmonary complications. The development of ARDS or the related entity of lung injury is associated with prolonged hospitalisation, ventilation, and time spent in intensive care, and profoundly increases the risk of mortality and significant morbidity. Patients with, or at risk of ARDS and lung injury, must be identified, optimised and managed with sound intraoperative principles (particularly ventilation and fluid management) – with the specific aim of limiting harm. This review will focus on the diagnosis, pathophysiology, prevention and management of ARDS and lung injury in the perioperative period.

Keywords: acute lung injury, anaesthesia, ARDS, ventilation

Introduction

Pulmonary complications after surgery are common and are associated with significant cost. These complications lengthen hospitalisation, ventilation, and time spent in intensive care, and profoundly increase the risk of mortality and significant morbidity. Acute respiratory distress syndrome (ARDS), a life-threatening respiratory disease process characterised by hypoxaemia and reduced lung compliance,[1,2] is one of the more serious postoperative pulmonary complications. In its severe form, ARDS carries a mortality rate of 45%.[1,3] This concise review will focus on the diagnosis, pathophysiology, prevention and management of ARDS and the related entity of lung injury. The aim is to provide a broad overview of a complex clinical area.

Perioperative mechanical ventilation is one of the primary risk factors for the development of postoperative pulmonary complications; as many as one in four patients with normal lungs will develop some form of lung injury following mechanical ventilation.[2] In patients with lung injury or ARDS, further lung injury risk with mechanical ventilation is significantly greater. However, much of this damage can be attenuated by using appropriate ventilation strategies.

Pathophysiology

The pathophysiological mechanisms of ARDS vary depending on the causative pathology, but several common inflammatory pathways that subsequently cause alveolar damage are involved. These inflammatory processes cause endothelial damage, disrupt normal protective barriers, inhibit surfactant production and function, impair coagulation, and inhibit normal alveolar immunological responses.[4,5] Increased vascular permeability and damage to the pulmonary microvasculature results in fluid and neutrophil leakage into alveolar and interstitial tissue.[6] The result is impaired gas exchange due to damaged alveolar-capillary membranes, and the two hallmark features of ARDS: hypoxaemia and reduced lung compliance.[1] These lung changes are rarely homogenous and result in areas of disease interspersed with normal lung units. The stretching at the interface of diseased and healthy lung also causes excessive shear stress and perpetuates the release of inflammatory mediators and exacerbates local and systemic inflammation.

Diagnostic criteria

In 2012 the Berlin Definitions replaced the 1994 American-European Consensus Conference (AECC) definition of 'acute lung injury' (ALI).[1,7] The term ALI was discarded and the distinction between primary and secondary ALI (largely related to onset time) was integrated into a new ARDS definition. The Berlin Definitions, compiled by the European Society of Intensive Care Medicine and endorsed by the American Thoracic Society and the Society of Critical Care Medicine, recognise three stages of severity based on the PaO_2/FiO_2 ratio.[8] Four factors are involved in making the diagnosis:

(a) Timing – onset over less than seven days;
(b) Chest x-ray (or computerised tomography [CT] scan) changes – bilateral opacification not explained by alternative lung pathology;
(c) Origin of oedema – must not be fully explained by cardiac failure or fluid overload, and an objective assessment (cardiac ultrasound) should be performed if there is uncertainty;
(d) Severity of hypoxaemia, graded according to PF ratio (p_aO_2 in mmHg), with a minimum positive end-expiratory pressure (PEEP) of 5 cm H_2O [mild (200–300), moderate (100–200) or severe (< 100)].[1]

Anaesthetic management strategies for patients with ARDS

Several advancements have improved ARDS outcomes. These include better ventilation strategies and care bundles, transfusion and fluid management, and early appropriate management of sepsis.[9–18] Patients with, or at risk of ARDS, must be identified, optimised and managed with sound intraoperative principles

(particularly ventilation and fluid management) – with the specific aim of limiting harm.

Anaesthesiologists caring for patients with, or at risk of ARDS, should aim to:
(1) Provide optimal ventilation and anaesthesia without compromising the cardiovascular system;
(2) Ventilate patients with lung protective strategies to limit inflammatory processes;
(3) Avoid unnecessary intravenous fluids that contribute to extravascular lung water accumulation; and
(4) Promote recovery and postoperative mobilisation.

Despite a lack of data showing that these principles improve outcomes in healthy patients, it seems prudent to adopt these strategies in all ventilated perioperative patients.

A. Preoperative management

Preoperative objectives include the identification of patients at risk for developing ARDS (using general risk factors and scoring systems) and optimisation of these patients where possible. These measures are outlined below.

(1) Identification of general risk factors for developing ARDS (Table 1).

Table 1: General risk factors for developing ARDS[1]

Direct risk factors	Indirect risk factors
Pneumonia	Non-pulmonary sepsis
Aspiration of gastric contents	Major trauma
Inhalational injury	Pancreatitis
Pulmonary contusion	Severe burns
Pulmonary vasculitis	Non-cardiogenic shock
Drowning	Drug overdose
	Multiple transfusions or TRALI

Notes: ARDS = acute respiratory distress syndrome; TRALI = transfusion-associated acute lung injury.

(2) Risk prediction scores for ARDS.

(a) Several ARDS risk prediction models exist and vary from specific surgical populations (predominantly cardiothoracic)[19–25] to general surgical patients.[26,27] The Surgical Lung Injury Prediction 2 model (SLIP-2) is a mathematical model that predicts patients at risk of developing early postoperative lung injury (Table 2). The score performed well in distinguishing patients that develop early lung injury from those that do not (AUC [95% CI], 0.84 [0.81, 0.88]).[27] Kor et al.[27] identified nine independent ARDS predictors.

(b) The Lung Injury Prediction (LIP) Score is an alternative model initially developed for all patients, and validated in surgical critical care patients.[28,29] The LIP Score performed well in this surgical population (receiver operating characteristic [ROC] area under the curve of 0.79, with good calibration).

(c) More recently, early oxygen saturation to fraction of inspired oxygen ratio (within 6 hours of hospital admission) has been shown to be an independent indicator of ARDS development in patients at risk.[30]

Table 2: Independent ARDS predictors used in the Surgical Lung Injury Prediction 2 model (SLIP-2)

SLIP-2 model predictors of ARDS[27]
Sepsis
High-risk aortic vascular surgery
High-risk cardiac surgery
Emergency surgery
Cirrhosis
Admission location other than home
Increased respiratory rate (20–29 and > 30 breaths/min)
FiO_2 greater than 0.35
SpO_2 less than 95%

Notes: ARDS = acute respiratory distress syndrome; FiO_2 = fraction of inspiratory oxygen; SpO_2 = blood oxygen saturation.

(d) Several biomarkers of alveolar epithelial injury, vascular endothelial injury and increased coagulation in patients with ARDS correlate with morbidity and mortality.[8,18,31] Biomarker panels may also help differentiate severe sepsis-induced ARDS from trauma-induced lung injury.[18,32–34] However, their clinical utility for diagnosis and prognostication is unproved.

(3) Optimisation

(a) Early recognition of underlying respiratory infections and identification of causative pathogens is an essential part of preoperative management. Consideration should be given to possible bacterial, fungal and viral infections. Early empiric antibiotic therapy is advisable in overtly septic patients, with subsequent de-escalation to directed therapy in response to culture results.

(b) Bedside lung ultrasound may offer additional diagnostic information as shown in a recent pilot study combining ultrasound with SpO2/FiO2 ratios.[35] It is also a useful adjunct to help differentiate ARDS from cardiogenic pulmonary oedema.[36]

(c) Routine approaches to reduce gastric aspiration and ventilator-associated pneumonia should be employed.

B. Intraoperative management

General anaesthesia has several negative consequences on the respiratory system:

(i) Basal atelectasis (due to positioning, high inspired FiO_2, and reduced functional residual capacity).
(ii) Loss of muscle tone and subsequent decreased negative pressure lung expansion.
(iii) Decreased minute ventilation.
(iv) Closing capacity nearing functional residual capacity.
(v) Volatile anaesthetic-induced inhibition of hypoxic pulmonary vasoconstriction leading to increased intrapulmonary shunting.
(vi) Increased alveolar dead space ventilation due to atelectasis and alterations in perfusion characteristic in the supine and anaesthetised position.
(vii) Blunting of the normal responses to hypercarbia.[37]

Ventilating patients with ARDS undergoing general anaesthesia adds even more complexity.

(1) Ventilation

Mechanical forces generated by positive pressure ventilation contribute to ventilator-induced lung injury and ARDS. This is particularly severe at the interface between normal lung units and diseased lung units. Management strategies attempt to limit the amount of stretching, strain and biotrauma generated at these interfaces.[38] Newer concepts in reducing ventilator-induced lung injury include minimising alveolar damage through the reduced transfer of energy to at-risk lung units. Recent focus has moved away from traditional concepts such as barotrauma and volutrauma, towards mechanical and driving power. Driving pressure (the plateau pressure minus PEEP) is once such theory that explores the relationship between reduced energy transfer and improved mortality in perioperative and ARDS patients. Although further research is required, it is a promising field that is supported by both physiological explanations and retrospective data analysis. Mechanical power is a concept that attempts to unify multiple ventilator-related causes of lung injury into a single variable.[39] Ventilator indices such as tidal volume, driving pressure, flow, PEEP and respiratory rate are expressed in an equation that quantifies mechanical power, measured in joules. Initial experimental work has confirmed that with rising power there is a higher likelihood of developing ventilator-induced lung injury (VILI).[40] Driving power and mechanical power are increasingly being suggested as new targets in ventilator strategies aimed at reducing VILI. A detailed discussion is beyond the scope of this review, but further reading is advised in this area.[41]

(a) *FiO_2*: The majority of evidence from ICU patients now recommends targeting an FiO_2 resulting in a SpO_2 of between 88 and 95%.[36] Additional research is needed to determine the net benefits related to potential lung toxicity caused by unnecessarily high concentrations of inspired oxygen (such as diffuse alveolar damage, direct airway injury, increasing dead space), and the potential benefits on neurocognitive outcomes when targeting normoxaemia.[42]

(b) *Positive end expiratory pressure* (*PEEP)*: Selecting the ideal PEEP is challenging. PEEP maintains open alveolar units, and potentially avoids repeated opening and closing of alveoli and interfaces between collapsed and open units. This minimises sheer forces and biotrauma experienced in an unevenly atelectatic lung. However, in heterogeneously affected lungs, where PEEP may be beneficial in some lung units, excessive PEEP may result in overdistension. It may be reasonable to apply a PEEP of 10 cmH_2O at the start of ventilation.[36,43–45]

(c) *Tidal volumes (TV)*: Increasing data support low tidal volume ventilation in patients with established ARDS. Despite a lack of randomised control trials showing a related decrease in postoperative pulmonary complications,[43] low tidal volumes are likely to reduce the shear stresses imposed by PPV within diseased lung regions, and this approach has the potential to improve outcomes.[36,46] Increasing importance is being placed on the measurement and control of the driving pressure (ratio between tidal volume and compliance, or plateau pressure minus PEEP).[47–49] Tidal volumes of 6–8 ml/kg (importantly, ideal ventilatory body weight) should be targeted, with a low plateau pressure (< 16 cm H_2O), and preferably a low ΔP (< 13 cm H_2O). Tidal volumes of 4–5 ml/kg or less should be targeted for one lung ventilation. If achieving ventilator targets described above does not allow normalisation of p_aCO_2, permissive hypercapnia in the absence of raised intracranial pressure or severe right heart failure should be allowed. The physiological benefits of hypercapnia include a rightward shift of the oxygen-haemoglobin dissociation curve, increased cardiac output and an anti-inflammatory action.[50]

(d) *Mode of ventilation*: The mode of ventilation does not appear to influence ARDS outcomes.[51,52]

(e) *Recruitment manoeuvres*: Recruitment manoeuvres are controversial, being recommended by some and avoided by those supporting 'intraoperative permissive atelectasis'.[45,53] This new concept suggests recruitment manoeuvres should not be routine, particularly in severe ARDS. Recruitment manoeuvres may also be associated with significant haemodynamic instability due to effects on right ventricular preload and afterload. Recommendations support individualised practice and avoidance of unnecessary attempts to expand lung units and the worsening of biotrauma and atelectrauma.[53] The benefit of recruitment manoeuvres on patient outcome remain inconclusive,[54] and, as a recent publication suggests, may even increase mortality in patients with moderate to severe ARDS.[55]

(f) *Fluid management*:

(i) Although maintaining adequate tissue perfusion is important, excess intravenous fluid potentially worsens hypoxaemia, as leakage through a dysfunctional endothelial lung barrier increases extravascular lung water. Intravenous fluids should be given judiciously, guided by regular and repeated volume assessments and assessment of fluid responsiveness. Dynamic markers of fluid responsiveness are superior to static markers and should be incorporated in the routine assessment of perioperative patients. Xiaoming *et al*. demonstrated that a large positive net fluid balance – independent of ventilator settings, plasma transfusions and severity of disease – was a risk factor for ARDS.[56]

(ii) Blood product transfusions (red blood cells, plasma and platelets) have been identified as risk factors for ARDS. In the ICU and when possible in the operating room, a restrictive transfusion strategy with a haemoglobin transfusion trigger of 7 g/dl and target haemoglobin of > 7 g/dl should be used. Transfusion-related acute lung injury has been linked to plasma containing blood products (platelets, fresh frozen plasma).[57] While efforts in the developed world aim to screen for high-risk donors, this is usually not possible in the developing world.[18,58,59]

(2) Anaesthetic choices

(a) Inhalational anaesthetics: In animal models, volatile anaesthetic agents protect against the damage caused during ischaemic-reperfusion injury.[60] The benefit may be multifactorial and includes protection against endothelial glycocalyx degradation, ischaemic pre-conditioning,

and even immune-modulating effects (inhibition of pro-inflammatory mediators including IL-8, IL-10, and TNF).[8,61–66]

(b) There is little evidence to support one type of anaesthetic over another. Volatile anaesthetic agents do inhibit hypoxic pulmonary vasoconstriction, but carry potential advantages mentioned above. Intravenous agents, such as propofol, may worsen endothelial function when given in overdose, but this requires further research.[67]

(c) There is little evidence to guide the choice of anaesthesia with a view to reducing the postoperative complications of ARDS. However, a general anaesthetic is likely to be appropriate for most ARDS patients, as management of PEEP and TV generally requires tracheal intubation. There is some evidence supporting the approach of a combined general anaesthetic and neuraxial technique for postoperative analgesia as it has been shown to decrease the incidence of postoperative pneumonia and respiratory failure – potential triggers for ARDS[68] – although the benefits of neuraxial block and postoperative epidural are not universal.[69]

(3) Haemodynamics

(a) Haemodynamic instability may occur during anaesthesia for ARDS. Potential causes are multifactorial and occur at least in part because of an interdependent functional relationship between the respiratory and cardiovascular systems. Right heart dysfunction or failure may result from pulmonary arterial hypertension secondary to hypoxic pulmonary vasoconstriction, exacerbated by the negative effects of mechanical ventilation on the right side of the heart, i.e. increased pulmonary vascular pressure from PEEP and positive pressure ventilation. Ventricular interdependence (interventricular septal shift that results from right ventricular failure and distension, impedes left ventricular (LV) filling and therefore preload), may also induce systemic hypotension. Increased pleural pressure may reduce venous return, especially in hypovolaemic patients. The poorly explained negative inotropic effects caused by the systemic inflammatory response may additionally exacerbate cardiovascular system failure.

Increased LV diastolic pressure caused by intraventricular septal shift to the left side may increase pulmonary venous pressure, increasing capillary hydrostatic pressure and subsequent

Table 3: Modalities of therapy investigated for ARDS management

Therapy	Comment
Corticosteroids[71–76]	Identification of 21 microRNA has suggested steroid-sensitive and steroid-independent mechanisms in the development of ARDS. This may account for different responses to the use of corticosteroids in previous studies
Inhaled vasodilators[36,77]	Nitric oxide has vasodilatory effects on pulmonary vasculature, and improves arterial oxygenation, but its use has not demonstrated mortality or significant outcome benefits. Its use is complicated by high costs and increased renal dysfunction
Muscle relaxants[36,78,79]	Short-term use of muscle relaxation (up to 48 h) for patients with severe ARDS may reduce mortality risk and reduce ventilator-associated lung injury. This may be mediated by reducing transpulmonary pressures during mechanical ventilation and reducing oxygen consumption, but this strategy requires further investigation
ECMO[80]	ECMO has shown promising results in uncontrolled reports of its use in the management of severe ARDS. The role of this expensive therapy in ARDS treatment and in the transport of those with severe ARDS requires further investigation
Aspirin[81]	Aspirin may have positive effects on platelets that play an active role in the development of ARDS. The Lung Injury Prevention Study with Aspirin, a phase II trial, did not show any outcome benefit
Aerosolised beta-2-agonists	These agents have previously been effective in reducing pulmonary oedema by stimulating cyclic adenosine monophosphate-dependent alveolar fluid clearance. Initial studies demonstrated harm in patients with ARDS.[82–84] However, a recent study showed favourable results with inhaled budesonide and formoterol. Patients had improved oxygenation, lower rates of acute respiratory failure and ARDS.[85] This therapy appears promising
Keratinocyte growth factor and mesenchymal stem cells	Keratinocyte growth factor (KGF) is expressed by mesenchymal cells and appears to promote cell repair via several mechanisms including stimulating type-2 pneumocyte development, increased surfactant production, DNA repair, and improved alveolar fluid clearance.[18,86,87] The effects of KGF may explain the possible benefits of mesenchymal stem cells in ARDS. Researchers are currently investigating the role of intravenous KGF in patients with ARDS, and the immunomodulating role of mesenchymal stem cells[88]
Surfactant	Surfactant inhibition and degradation is an important contributor to the pathogenesis of ARDS. Although successful in neonates and infants, multiple large trials in adults failed to show improved clinical outcomes, despite reports of transient improvements in oxygenation and lung function. There is a continued search for a better exogenous surfactant replacement therapy[89,90]
Beta-blockers	The theoretical benefit of beta-blockers in ARDS involves suppression of the overstimulated sympathetic response that may negatively affect pulmonary vasculature.[91] Some benefit has been demonstrated in a porcine endotoxin shock model; however, further RCTs are required to understand benefit[92]

Notes: ARDS = acute respiratory distress syndrome, ECMO = extracorporeal membrane oxygenation, DNA = deoxyribonucleic acid.

extravascular lung water extravasation.[70] The authors of a recent review emphasise the importance of ensuring euvolaemia, without unnecessary use of intravenous fluid administration. Bedside echocardiography, transpulmonary thermodilution, and inotropic support may provide additional monitoring information. Right ventricular ventilation protection strategies include minimising driving pressures, providing PEEP and ensuring adequate oxygenation. [70]

Questions and future developments

Table 3 outlines several potential new strategies based on putative pathophysiological mechanisms for the management of ARDS. None have been shown to provide a definitive clinical benefit.

Prone positioning may benefit oxygenation due to the heterogenous atelectasis and consolidation seen in ARDS. Despite mortality benefit in the PROSEVA and other trials, its use in the perioperative period is unrealistic in most circumstances.[93]

Conclusion

Lung injury is a common pathology facing anaesthesiologists and accounts for significant postoperative pulmonary complications. Pulmonary and systemic complications can possibly be limited with appropriate ventilatory, haemodynamic and preoperative and postoperative critical care management bundles. New research is exploring multiple approaches to preventing and treating ARDS. These include optimisation of mechanical ventilation settings to minimise injury from positive pressure ventilation (pressures and volumes), pathophysiological mechanisms (inflammatory mediation), and supportive care (fluid therapy), and even alternative methods of respiratory support (ECMO).

Summary and learning points

(1) Anaesthesiologists can play a potentially important role in preventing ARDS occurring postoperatively by applying preventive strategies, and minimising the complications of mechanical ventilation in patients with ARDS presenting for operation.

(2) ARDS management strategies should be implemented throughout the preoperative, intraoperative and postoperative periods.

(3) Ventilation goals in patients with ARDS presenting for anaesthesia should include: minimise F_iO_2 to maintain SpO_2 above 88%; appropriate PEEP to avoid atelectasis, but sufficient to prevent shear stress; consider lowering PEEP if the driving pressure is high, particularly if increasing PEEP increases driving pressure, or there are other signs of overdistension present; maintain low tidal volumes (6 ml/kg ideal body weight); a plateau pressure < 16 cmH_2O (maximum 30 cmH_2O); and a low ΔP (< 13 cm H_2O), even if the resulting low TV requires permissive hypercapnia.

(4) Avoid excessive intraoperative transfusion with goal of targeting 7 g/dl in the postoperative ICU period.

(5) Volatile anaesthetics may provide a theoretical protective function, despite the negative effects on hypoxic pulmonary vasoconstriction.

(6) Haemodynamic stability should be achieved though continuous volume status assessment and judicious inotropic therapy. Utilisation of bedside investigations such as echocardiography, and transpulmonary thermodilution/cardiac output monitoring may provide additional guidance for fluid and vasopressor management.

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ORCID

Robert Wise http://orcid.org/0000-0001-5237-5582
Gavin Joynt http://orcid.org/0000-0002-5823-3435
Reitze Rodseth http://orcid.org/0000-0002-3779-7805

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