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Acute respiratory distress syndrome following cardiovascular surgery: current concepts and novel therapeutic approaches

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Abstract

Purpose of review—This review gives an update on current treatment options and novel concepts on the prevention and treatment of the acute respiratory distress syndrome (ARDS) in cardiovascular surgery patients.

Recent findings—The only proven beneficial therapeutic options in ARDS are those that help to prevent further ventilator-induced lung injury, such as prone position, use of lung-protective ventilation strategies, and extracorporeal membrane oxygenation. In the future also new approaches like mesenchymal cell therapy, activation of hypoxia-elicited transcription factors or targeting of purinergic signaling may be successful outside the experimental setting. Owing to the so far limited treatment options, it is of great importance to determine patients at risk for developing ARDS already perioperatively. In this context, serum biomarkers and lung injury prediction scores could be useful.

Summary—Preventing ARDS as a severe complication in the cardiovascular surgery setting may help to reduce morbidity and mortality. As cardiovascular surgery patients are of greater risk to develop ARDS, preventive interventions should be implemented early on. Especially, use of low tidal volumes, avoiding of fluid overload and restrictive blood transfusion regimes may help to prevent ARDS.

Keywords

acute respiratory distress syndrome; cardiovascular surgery; inflammation; lung

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

The 2012 published Berlin Definition describes the acute respiratory distress syndrome (ARDS) as hypoxemia, occurring within 1 week of a known risk factor or worsening of respiratory symptoms, associated with bilateral opacities in at least three quadrants on chest radiograph, that cannot be fully explained by pleural effusions or atelectasis. Cardiac failure or fluid overload as the only reason for the bilateral infiltrates needs to be excluded. Three subcategories of ARDS have been proposed, based on the severity of hypoxemia [mild ($200 \text{ mmHg} < \text{PaO}_2/\text{FIO}_2 \leq 300 \text{ mmHg}$), moderate ($100 \text{ mmHg} < \text{PaO}_2/\text{FIO}_2 \leq 200 \text{ mmHg}$), and severe ($\text{PaO}_2/\text{FIO}_2 \leq 100 \text{ mmHg}$)] [1].

Cardiac surgery is a known risk factor for ARDS, especially when using cardiopulmonary bypass (CPB), because CPB induces a systemic inflammatory response and pulmonary ischemia-reperfusion injury. Today more high-risk patients undergo cardiac surgical interventions and an increasing number of patients is provided with complex procedures [2,3]. To date there are eight clinical studies that analyzed the incidence, risk factors, and mortality of ARDS following cardiac surgery (overview in [4]). The incidence of ARDS varied from 0.17 to 2.5% and mortality from 15 to 91.6%. Most studies investigated patients after coronary artery bypass grafting, valve, and combined surgery, one study included patients after isolated coronary bypass and one reported data about off-pump coronary bypass grafting. The large variations in mortality are a result of differences in study population, study design and used definitions of ARDS, and illustrate how difficult it can be for clinicians to predict the risk for an individual patient after cardiovascular surgery to develop ARDS. However, only if a patient at risk is identified early the complications and the high mortality of severe ARDS might be avoided.

KEY POINTS

- ARDS is a rare but serious complication after cardiovascular surgery.
- Strategies to prevent VILI, like ventilation with low tidal volumes and in severe cases prone position and/or ECMO are currently the only therapeutic options reducing mortality in ARDS.
- Clinical trials currently under investigation might provide new pharmaceutical therapies like mesenchymal cell therapy in ARDS. Ongoing basic research on targeting hypoxia-inducible factor (HIF) and purinergic signaling during ARDS may reveal future treatment options.
- Prediction scores and biomarkers could help to identify at-risk patients for the development of ARDS. Preventing rather than treating ARDS may be the key to reduce mortality of this severe and complex disease.

Current therapeutic concepts of acute respiratory distress syndrome

Despite great effort to improve outcomes in ARDS, the only therapeutic measure shown to decrease mortality is lowering the risk for ventilator-induced lung injury (VILI) by using low tidal volume ventilation [5] and prone positioning [6]. In extreme, life threatening cases,

extracorporeal membrane oxygenation (ECMO) seems to serve as a bridge to recovery as it enables lung-protective ventilation [7^{*}]. Apart from prevention of VILI, there are additional supportive interventions like restrictive fluid and transfusion strategies and inhaled pulmonary vasodilators.

Lung-protective ventilation

Low tidal volume (6 ml/kg of predicted body weight), limitation of plateau pressure (less than 28–30 cm H₂O), and appropriate positive end-expiratory pressure (PEEP) levels are crucial to prevent further injury during ARDS [5]. Meanwhile, lung-protective ventilation strategies are standard practice for the management of ARDS. During the pandemic influenza A/H1N1 outbreak 2009/2010 in the Republic of Korea, Oh *et al.* [8] conducted a retrospective observational study of 104 patients with ARDS caused by viral pneumonia. Patients with tidal volumes less than or equal to 7 ml/kg required ventilators, ICU admissions, and hospitalizations for fewer days than those with tidal volumes greater than 7 ml/kg. Tidal volumes greater than 9 ml/kg and Sequential Organ Failure Assessment score were significant predictors of 28-day ICU mortality [8]. This study adds reliable evidence that lung-protective ventilation is also useful in patients with ARDS from viral etiologies.

Prone position

Prone positioning is not only able to improve oxygenation by increasing alveolar recruitment and enhancing ventilation-perfusion matching but also prevents VILI. In severe ARDS, prolonged (at least 16 h) prone-positioning sessions significantly decrease mortality [6]. Two recent meta-analyses found that prone position significantly improved survival, when combined with low tidal volume strategy and all-cause mortality decreased when the duration of prone was prolonged (>16 h/day), particularly in patients with severe ARDS [9^{*}, 10^{*}].

In cardiovascular surgical patients, effects of prone positioning on hemodynamics and heart function are of special interest. Guerin *et al.* [11] give an overview of hemodynamic studies in prone positioning in ARDS patients showing the beneficial and potential adverse effects and the underlying mechanisms. Of special importance may be the reduction of the transpulmonary gradient as vascular dysfunction is an independent risk factor for ARDS mortality. Additionally, prolonged prone positioning can reduce right ventricle pressure overload, decreases mean right ventricle enlargement and reduces septal dyskinesia as studied in 42 patients with severe ARDS treated by prone positioning to correct severe oxygenation impairment [12]. By collecting hemodynamic, respiratory, intra-abdominal pressure, and echocardiographic data from 18 patients with ARDS under protective ventilation and maximal alveolar recruitment, Jozwiak *et al.* [13] were able to show that prone positioning increased the cardiac preload, decreased the right ventricular afterload, and increased the left ventricular afterload. These effects resulted in an increase in cardiac index only in patients with preload reserve, emphasizing the important role of preload in the hemodynamic effects of prone positioning [13].

However, in obese patients prone position can have detrimental effects, because an increase of intra-abdominal pressure may worsen splanchnic perfusion. In a recently published

retrospective study, a significant interaction effect between abdominal obesity and prone position with respect to overall mortality risk, renal failure, and hypoxic hepatitis was seen [14].

Extracorporeal membrane oxygenation

Evolution of ECMO technology such as smaller systems and cannulation in peripheral hospital sites by mobile ECMO teams before transfer to ARDS centers offer a perspective for improve outcomes in appropriately selected patients with severe ARDS [7^{*}]. Further research is needed regarding the timing of the initiation of ECMO, the standardization of therapy and monitoring, and selection of patients who will benefit most from venovenous ECMO. The results from an ongoing randomized controlled trial (ECMO to rescue lung injury in severe ARDS, EOLIA) will contribute valuable data to guide clinical decisions for the use of ECMO therapy.

Another important question is, what ventilation strategy should be used once a patient is supported with venovenous ECMO. A recent international survey revealed significant variations in ventilator settings during ECMO [15]. Because proper gas exchange is achieved extracorporeally, invasive ventilator settings can be minimized to avoid further baro and biotrauma by VILI. However, it is unclear whether minimal (or no) tidal volume [16], resulting in near complete atelectasis, are more lung protective than a ventilation pattern with a lung recruitment strategy.

Furthermore, a combination of prone positioning and venovenous ECMO was shown to be feasible [17], but larger studies are necessary to determine reduction in mortality.

Lastly, in addition to short-term survival, it is equally important to follow ECMO survivors to evaluate long-term outcomes and quality of life [18].

Fluid management

ARDS is characterized by protein-rich lung edema that can be aggravated by development of pulmonary hypertension, increased pulmonary capillary pressure and cardiac failure, especially in cardiovascular patients with pre-existing conditions. Additionally, mechanical ventilation with positive intrathoracic pressure further induces salt and water retention, while impairing alveolar fluid clearance. Clinical trials have shown that after achieving hemodynamic stability, limitation of fluid intake in combination with diuretic treatment improved oxygenation, and reduced length of mechanical ventilation [19]. These results support the use of a conservative strategy of fluid management in ARDS patients. However, a possible complication associated with conservative fluid management may be long-term cognitive impairment [20]. Underlying diseases (e.g., presence or absence of sepsis) and relevant comorbidities (e.g., right heart failure, pulmonary hypertension, chronic renal failure) have to be taken into account.

Optimized transfusion regime

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related mortality. The incidence of TRALI is much higher in patients undergoing cardiac surgery than in the general hospital population and contributes to an adverse outcome [21].

Erythrocyte, platelet, and plasma transfusions are independent risk factors for ARDS [22–24]. Anemia and transfusion are associated with adverse effects and increased morbidity in cardiac surgery patients, therefore defining the optimal transfusion thresholds is crucial [25^{***}]. Further, large prospective studies are needed to determine the ideal transfusion algorithms in this high-risk patient population.

In the past decade, blood banks have implemented low-risk TRALI donor strategies, including a male-only donor policy for plasma-containing blood products to prevent onset of TRALI. A meta-analysis using a random-effects model, including all transfused products showed a significant reduction for the risk of TRALI after implementation of low-risk TRALI donor strategies in patient populations prone to develop TRALI [26^{*}].

Neuromuscular blockade

The usefulness of neuromuscular blocking agents (NMBAs) during the course of ARDS remains controversial. In acute severe ARDS, NMBAs might reduce patient-ventilator asynchrony, with a better control of tidal volume, leading to a decrease of baro, volu, and atelectotrauma. Additionally in early ARDS, NMBAs can decrease local and systemic concentrations of proinflammatory cytokines (i.e., biotrauma), assuming a possible direct anti-inflammatory effect of NMBAs [27]. Three clinical trials of a research group in France showed that the use of cisatracurium during early ARDS, especially in the most hypoxemic patients ($\text{PaO}_2/\text{FiO}_2 < 120 \text{ mmHg}$), improves oxygenation and decreases the 90-day mortality rate [27–29]. Short-term administration of NMBAs (less than 48 h) does not appear to be an independent risk factor for ICU-acquired weakness [30]. However, extended length of infusion time, high dosage, combination with corticosteroids or use in patients with hyperglycemia, renal or hepatic dysfunction increase the risk of ICU-acquired weakness. A structural class effect may also exist, with aminosteroid NMBA agents (e.g., vecuronium, pancuronium, rocuronium) posing a higher risk of ICU-acquired weakness than benzyloquinolinium compounds (e.g., atracurium, cisatracurium, mivacurium) [31^{***}].

On the other hand, during mild ARDS, preservation of spontaneous breathing probably favors oxygenation, and therefore could decrease total length of mechanical ventilation [31^{***}]. So far, hard criteria of when to use NMBAs and controlled ventilation versus preserving muscle activity to maintain spontaneous breathing modes are still missing and further studies are necessary.

Inhaled pulmonary vasodilators

The rationale of using inhaled pulmonary vasodilators is based on the characteristic symptoms of ARDS involving mismatching of ventilation and perfusion and pulmonary hypertension. In 2007, Adhikari *et al.* [32] conducted a meta-analysis of 12 trials with a total of 1237 patients showing that inhaled NO (iNO) is associated with limited improvement in

oxygenation in patients with ARDS and even in severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 100 \text{ mmHg}$) has no beneficial effect on mortality. It may even cause harm by promoting renal dysfunction, and therefore increasing mortality. The use of iNO should only be considered if all other possibilities of supportive treatments like prone ventilation and ECMO have been exploited.

Synthetic prostaglandin analogs can bind to four pulmonary prostanoid receptors that have been identified to be involved in regulating vascular tone, platelet activation, and immunological cell responses. Compared with iNO, inhaled prostanoids require no special application and monitoring equipment, and are therefore easier and less expensive to administer. This could be the reason for the increase in use over time in the treatment of ARDS [33], although there is no clinical data showing a mortality benefit and large scale randomized clinical trials (RCTs) are lacking [34]. In a meta-analysis in 2015, Fuller *et al.* [34] demonstrate that inhaled prostaglandins improve oxygenation and decrease pulmonary artery pressures. On the other hand, they also lower systemic pressure, with hypotension occurring in 17.4% of patients in observational studies [34]. Three of the 25 studies included reported thrombocytopenia, anemia, or transfusion requirement. Owing to so far limited data on clinical benefit but possible harm, the use of inhaled prostaglandins in ARDS needs further investigation.

Novel therapeutic concepts

Despite more than 150 RCTs and 29 meta-analyses of multiple potential therapies, the only interventions for ARDS shown to reduce mortality are those minimizing VILI [35^{***}]. This ‘translational failure’ may be because of heterogeneous patient populations and the complex disease pathogenesis. Curley and Laffey [36^{***}] provide a detailed overview of a number of ongoing ARDS trials and promising pharmaceutical therapies currently under investigation. In this review, we present the results from already completed clinical trials and a selection of ambitious human and animal studies with the focus on targeting HIF and purinergic signaling.

Mesenchymal cell therapy

Mesenchymal stem (stromal) cells (MSCs) regulate both innate and adaptive immune system and potentially inhibit the production of proinflammatory cytokines in ARDS [37]. Additionally, MSCs directly attenuate bacterial sepsis, a common cause of ARDS, by increasing bacterial clearance.

A recent pilot feasibility study of MSC treatment in ARDS patients demonstrated no adverse effects [38]. A recently published multicenter, open-label, dose-escalation, phase 1 clinical trial of allogeneic bone-marrow derived MSCs in patients with moderate-to-severe ARDS [Stem cells for ARDS treatment (START) trial] also showed no severe side-effects of MSC treatment [39]. Based on this phase 1 experience, the study has proceeded to phase 2 testing with a primary focus on safety and secondary outcomes, including respiratory, systemic, and biological outcomes [39].

Statins

HMG CoA-reductase inhibitors (statins) exert diverse pleiotropic effects beyond their primary effect in cholesterol reduction, including anti-inflammatory and endothelial protective effects, and therefore might be beneficial in ARDS. Two in 2014 published larger multicenter, double-blind phase 2/3 clinical trials of statin therapy [The hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in acute lung injury to reduce pulmonary dysfunction (HARP-2) investigators studied simvastatin in 540 ARDS patients recruited from general intensive care units in the UK and Ireland [40]. The ARDS Clinical Trials Network used rosuvastatin in 745 patients with sepsis-associated ARDS [41]] showed no improvement of outcomes in patients with ARDS. Rosuvastatin, a hydrophilic statin, not only did not improve 60-day in-hospital mortality or increase mean ventilator-free days but also may increase hepatic or renal dysfunction [41].

Hypoxia-inducible factor and purinergic signaling

Several studies suggest an important role for HIF or HIF-specific target genes in dampening lung inflammation during ARDS [42]. The detrimental effects of high inspiratory oxygen concentrations used during ARDS seem to be connected with an alteration of purinergic signaling events. Purinergic signaling events involve the activation of ATP/ADP and adenosine receptors. For example, anti-inflammatory adenosine is generated in the extracellular compartment as a breakdown product of ATP or ADP [43]. This pathway is under the enzymatic control of CD39 (conversion of ATP/ADP to AMP) and CD73 (conversion of AMP to adenosine). In an open-label study in patients with ARDS, recombinant IFN β -1a, which increases CD73 synthesis, was administered intravenously [44]. IFN β -1a upregulated human lung CD73 expression, and was associated with a reduction in 28-day mortality in patients with ARDS [44].

In several animal models and experimental settings, targeting adenosine receptors has been demonstrated to regulate endothelial and epithelial integrity, and polymorphonuclear cell trafficking in the lung [45,46]. Each type of adenosine receptor (A1, A2A, A2B, and A3) is characterized by a unique pharmacological and physiological profile and has a distinct expression pattern on different cell types. Pharmacologic agents that selectively target adenosine receptors are available, as well as tissue-specific gene-deficient mice, hopefully leading to future therapeutic strategies in ARDS [45].

Other possible beneficial impacts of HIF signaling could be achieved by application of HIF activators or stabilizers [47]. However, so far HIF activators like prolyl-hydroxylase inhibitors have not been used in a clinical setting in ARDS. Owing to studies implicating a functional role of HIFs expressed in alveolar epithelial cells, it is conceivable that HIF activators could be given via an inhaled route. As such, systemic effects of HIF activators could be minimized, while simultaneously achieving a sufficient concentration to stabilize HIFs in the target cell population [42].

Prevention of acute respiratory distress syndrome in high-risk cardiovascular surgery patients

Identifying patients at risk and implementing a preventive strategy for ARDS should be considered in all cardiovascular surgery patients.

In a recent population-based, nested, matched case-control study, Ahmed *et al.* demonstrated that inadequate empirical antimicrobial treatment, hospital-acquired aspiration, injurious mechanical ventilation, blood transfusion, and fluid administration were associated with the development of ARDS [48[¶]]. Exposure to antiplatelet agents during the at-risk period was associated with a decreased risk of ARDS [48[¶]]. Therefore, prevention of adverse hospital exposures in at-risk patients might decrease the incidence of ARDS.

Prediction scores in acute respiratory distress syndrome

Recently, several studies to identify patients who are at greatest risk for ARDS have been performed. Gajic *et al.* [49] developed the lung injury prediction score model for mixed medical and surgical patient populations. Similarly, for elective surgical populations the surgical lung injury prediction (SLIP) algorithm was developed by Kor *et al.* [50], unfortunately this score performs poorly in a context of high-risk surgical procedures, including emergency surgeries. A subsequent SLIP-2 model was developed that is able to effectively discriminate risk for postoperative ARDS in a multicenter cohort [51[¶]]. Nine independent predictors of ARDS were identified: sepsis, high-risk cardiac surgery, high-risk aortic vascular surgery and emergency surgery, cirrhosis, admission location other than home, increased respiratory rate (20–29 and ≥ 30 breaths/min), FiO₂ greater than 35%, and SpO₂ less than 95% [51[¶]].

Pre-emptive lung-protective ventilation

Recent meta-analyses and clinical trials have shown that pre-emptive application of protective ventilation in both high-risk ICU and surgery patients can reduce the incidence of ARDS [52,53[¶],54–56]. Furthermore, as Nieman *et al.* [57^{¶¶}] stated, mechanical ventilation could be used pre-emptively as a therapeutic tool to prevent ARDS progression. The use of protective ventilation strategies in at-risk patients well before any overt clinical signs of ARDS are present might reduce the incidence of ARDS.

Biomarkers of acute respiratory distress syndrome

The receptor for advanced glycation end products (RAGE) seems to be pivotal in the proinflammatory response in ARDS, and therefore is a candidate for an ARDS biomarker. RAGE is a multiligand pattern recognition receptor that is highly expressed in lung epithelium [58,59^{¶¶}]. Its ligation with damage-associated molecular pattern DAMP molecules, including high-mobility group box 1 (HMGB1) and S100A12 is thought to contribute to a pro-inflammatory response. Müller *et al.* studied whether damage-associated molecular pattern molecules are involved in the pathogenesis of TRALI in cardiac surgery patients. Unfortunately, they failed to prove that HMGB1 and soluble RAGE contributed to the development of TRALI. However, S100A12 is associated with duration of CPB, pulmonary inflammation, hypoxia and prolonged mechanical ventilation and may contribute

to acute lung injury in cardiac surgery patients [60]. Jabaudon *et al.* [61] showed that higher plasma levels of RAGE were strongly associated with impaired alveolar fluid clearance, indicative of the severity of lung epithelial injury. Panels of bio-markers might reflect multiple aspects of the complex pathophysiology of ARDS. For example, a panel that included inflammatory and lung epithelial injury markers (RAGE, surfactant protein D, and club cell protein 16) was useful to diagnose ARDS in severe sepsis [62].

CONCLUSION

ARDS is a rare but serious complication after cardiovascular surgery and despite innovative therapeutic efforts mortality remains high. Low tidal volume ventilator strategies and for severe cases prone position and/or application of ECMO can improve outcome by lowering the risk for VILI. Reducing the amount of transfusions whenever safe may also lower mortality. In the future, basic research uncovering the mechanisms of ARDS pathogenesis and ongoing clinical trials of novel therapies may reveal new treatment options. Prediction scores and possibly biomarkers, can help to identify high-risk patients. ARDS develops slowly over time that gives us the chance to block its progression early on, reducing the chances of development of severe forms of ARDS with a high mortality. Given the number of patients undergoing cardiovascular surgery, efforts to decrease the risk of ARDS could significantly decrease morbidity and mortality in this high-risk patient cohort.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ of outstanding interest

1. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012; 307:2526–2533. [PubMed: 22797452]
2. Teo KK, Cohen E, Buller C, et al. Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology/Canadian Society of Cardiac Surgery position statement on revascularization: multivessel coronary artery disease. *Can J Cardiol*. 2014; 30:1482–1491. [PubMed: 25475448]
3. Baillot RG, Joannis DR, Stevens LM, et al. Recent evolution in demographic and clinical characteristics and in-hospital morbidity in patients undergoing coronary surgery. *Can J Surg*. 2009; 52:394–400. [PubMed: 19865574]
4. Kogan A, Preisman S, Levin S, et al. Adult respiratory distress syndrome following cardiac surgery. *J Card Surg*. 2014; 29:41–46. A retrospective, observational study in the period between 2005 and 2013 on patients who underwent cardiac surgery. Previous cardiac surgery, complex

cardiac surgery, and more than three transfusions of packed red blood cells were independent predictors for the development of ARDS. [PubMed: 24299028]

5. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000; 342:1301–1308. [PubMed: 10793162]
6. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med.* 2013; 368:2159–2168. [PubMed: 23688302]
7. Lelgadowicz A, Fan E. Extracorporeal life support for severe acute respiratory distress syndrome. *Curr Opin Crit Care.* 2015; 21:13–19. A summary of the recent literature on ECMO in adults with severe ARDS, focusing on advances in equipment, current conventional and unconventional indications, complications, and future applications. [PubMed: 25517890]
8. Oh DK, Lee MG, Choi EY, et al. Low-tidal volume mechanical ventilation in patients with acute respiratory distress syndrome caused by pandemic influenza A/H1N1 infection. *J Crit Care.* 2013; 28:358–364. [PubMed: 23602273]
9. Sud S, Friedrich JO, Adhikari NK, et al. Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ.* 2014; 186:E381–E390. A meta-analysis and review showing that use of the prone position during mechanical ventilation improves survival among patients with ARDS who received protective lung ventilation. [PubMed: 24863923]
10. Beitler JR, Shaefi S, Montesi SB, et al. Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. *Intensive Care Med.* 2014; 40:332–341. A meta-analysis showing that prone positioning is associated with significantly reduced mortality from ARDS in the low tidal volume era. [PubMed: 24435203]
11. Guerin C, Baboi L, Richard JC. Mechanisms of the effects of prone positioning in acute respiratory distress syndrome. *Intensive Care Med.* 2014; 40:1634–1642. [PubMed: 25266133]
12. Vieillard-Baron A, Charron C, Caille V, et al. Prone positioning unloads the right ventricle in severe ARDS. *Chest.* 2007; 132:1440–1446. [PubMed: 17925425]
13. Jozwiak M, Teboul JL, Anguel N, et al. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2013; 188:1428–1433. [PubMed: 24102072]
14. Weig T, Janitza S, Zoller M, et al. Influence of abdominal obesity on multiorgan dysfunction and mortality in acute respiratory distress syndrome patients treated with prone positioning. *J Crit Care.* 2014; 29:557–561. [PubMed: 24666961]
15. Marhong JD, Telesnicki T, Munshi L, et al. Mechanical ventilation during extracorporeal membrane oxygenation. An international survey. *Ann Am Thorac Soc.* 2014; 11:956–961. [PubMed: 24983618]
16. Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO₂ removal versus ‘conventional’ protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive Care Med.* 2013; 39:847–856. [PubMed: 23306584]
17. Kredel M, Bischof L, Wurmb TE, et al. Combination of positioning therapy and venovenous extracorporeal membrane oxygenation in ARDS patients. *Perfusion.* 2014; 29:171–177. [PubMed: 23985422]
18. Hodgson CL, Hayes K, Everard T, et al. Long-term quality of life in patients with acute respiratory distress syndrome requiring extracorporeal membrane oxygenation for refractory hypoxaemia. *Crit care.* 2012; 16:R202. [PubMed: 23082772]
19. Wiedemann HP, Wheeler AP, Bernard GR. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med.* 2006; 354:2564–2575. [PubMed: 16714767]
20. Mikkelsen ME, Christie JD, Lanken PN, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med.* 2012; 185:1307–1315. [PubMed: 22492988]

21. Vlaar AP, Hofstra JJ, Determann RM, et al. The incidence, risk factors, and outcome of transfusion-related acute lung injury in a cohort of cardiac surgery patients: a prospective nested case-control study. *Blood*. 2011; 117:4218–4225. [PubMed: 21325598]
22. Khan H, Belsher J, Yilmaz M, et al. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *Chest*. 2007; 131:1308–1314. [PubMed: 17400669]
23. Jia X, Malhotra A, Saeed M, et al. Risk factors for ARDS in patients receiving mechanical ventilation for > 48 h. *Chest*. 2008; 133:853–861. [PubMed: 18263691]
24. Gajic O, Rana R, Winters JL, et al. Transfusion-related acute lung injury in the critically ill: prospective nested case-control study. *Am J Respir Crit Care Med*. 2007; 176:886–891. [PubMed: 17626910]
25. ■ Najafi M, Faraoni D. Hemoglobin optimization and transfusion strategies in patients undergoing cardiac surgery. *World J Cardiol*. 2015; 7:377–382. A review about patient blood management in cardiovascular surgery patients. [PubMed: 26225197]
26. ■ Muller MC, van Stein D, Binnekade JM, et al. Low-risk transfusion related acute lung injury donor strategies and the impact on the onset of transfusion-related acute lung injury: a meta-analysis. *Transfusion*. 2015; 55:164–175. A meta-analysis showing that the introduction of low-risk TRALI donor strategies for plasma-containing products results in a reduction of TRALI. [PubMed: 25135630]
27. Forel JM, Roch A, Marin V, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. *Crit Care Med*. 2006; 34:2749–2757. [PubMed: 16932229]
28. Gainnier M, Roch A, Forel JM, et al. Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. *Crit Care Med*. 2004; 32:113–119. [PubMed: 14707568]
29. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010; 363:1107–1116. [PubMed: 20843245]
30. Alhazzani W, Alshahrani M, Jaeschke R, et al. Neuromuscular blocking agents in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. *Critical care*. 2013; 17:R43. [PubMed: 23497608]
31. ■ Hraiech S, Yoshida T, Papazian L. Balancing neuromuscular blockade versus preserved muscle activity. *Curr Opin Crit Care*. 2015; 21:26–33. In this review, the authors discuss the benefits and disadvantages of the use of NMBAs versus the preservation of muscle activity and spontaneous breathing. [PubMed: 25517889]
32. Adhikari NK, Dellinger RP, Lundin S, et al. Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis. *Crit Care Med*. 2014; 42:404–412. [PubMed: 24132038]
33. Kredel M, Bierbaum D, Lotz C, et al. Therapy of acute respiratory distress syndrome: Survey of German ARDS centers and scientific evidence. *Anaesthesist*. 2015; 64:277–285. [PubMed: 25824000]
34. 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; 147:1510–1522. [PubMed: 25742022]
35. ■ Tonelli AR, Zein J, Adams J, et al. Effects of interventions on survival in acute respiratory distress syndrome: an umbrella review of 159 published randomized trials and 29 meta-analyses. *Intensive Care Med*. 2014; 40:769–787. A review looking for changes in mortality rate in published RCTs and meta-analyses ($n=20\,671$ patients) by therapeutical interventions for ARDS. Multiple interventions have been tested in ARDS, but low tidal volumes and prone positioning in severe ARDS seem to be the only effective. Most sporadic findings of interventions suggesting reduced mortality are not corroborated consistently in large-scale evidence, including meta-analyses. [PubMed: 24667919]
36. ■ Curley GF, Laffey JG. Future therapies for ARDS. *Intensive Care Med*. 2015; 41:322–326. A large review giving a detailed overview on ongoing ARDS trials and pharmaceutical therapies currently under investigation. [PubMed: 25472571]

37. Curley GF, Scott JA, Laffey JG. Therapeutic potential and mechanisms of action of mesenchymal stromal cells for acute respiratory distress syndrome. *Curr Stem Cell Res Ther.* 2014; 9:319–329. [PubMed: 24588087]
38. Zheng G, Huang L, Tong H, et al. Treatment of acute respiratory distress syndrome with allogeneic adipose-derived mesenchymal stem cells: a randomized, placebo-controlled pilot study. *Respir Res.* 2014; 15:39. [PubMed: 24708472]
39. Wilson JG, Liu KD, Zhuo H, et al. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase I clinical trial. *Lancet Respir Med.* 2015; 3:24–32. [PubMed: 25529339]
40. McAuley DF, Laffey JG, O’Kane CM, et al. Simvastatin in the acute respiratory distress syndrome. *N Engl J Med.* 2014; 371:1695–1703. [PubMed: 25268516]
41. Truitt JD, et al. National Heart L, Blood Institute ACTN. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. *N Engl J Med.* 2014; 370:2191–2200. [PubMed: 24835849]
42. Vohwinkel CU, Hoegl S, Eltzschig HK. Hypoxia signaling during acute lung injury. *J Appl Physiol.* 2015 Epub ahead of print.
43. Eltzschig HK, Sitkovsky MV, Robson SC. Purinergic signaling during inflammation. *N Engl J Med.* 2012; 367:2322–2333. [PubMed: 23234515]
44. Bellington G, Maksimow M, Howell DC, et al. The effect of intravenous interferon-beta-1a (FP-1201) on lung CD73 expression and on acute respiratory distress syndrome mortality: an open-label study. *Lancet Respir Med.* 2014; 2:98–107. [PubMed: 24503265]
45. Hoegl S, Brodsky KS, Blackburn MR, et al. Alveolar epithelial A2B adenosine receptors in pulmonary protection during acute lung injury. *J Immunol.* 2015; 195:1815–1824. [PubMed: 26188061]
46. Eckle T, Grenz A, Laucher S, et al. A2B adenosine receptor signaling attenuates acute lung injury by enhancing alveolar fluid clearance in mice. *J Clin Invest.* 2008; 118:3301–3315. [PubMed: 18787641]
47. Eltzschig HK, Bratton DL, Colgan SP. Targeting hypoxia signalling for the treatment of ischaemic and inflammatory diseases. *Nat Rev Drug Discov.* 2014; 13:852–869. [PubMed: 25359381]
48. Ahmed AH, Litell JM, Malinchoc M, et al. The role of potentially preventable hospital exposures in the development of acute respiratory distress syndrome: a population-based study. *Crit Care Med.* 2014; 42:31–39. Population-based, nested, matched case-control study aiming to determine the association between specific hospital exposures and the rate of ARDS among at-risk patients. [PubMed: 23982022]
49. Gajic O, Dabbagh O, Park PK, et al. Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. *Am J Respir Crit Care Med.* 2011; 183:462–470. [PubMed: 20802164]
50. Kor DJ, Warner DO, Alsara A, et al. Derivation and diagnostic accuracy of the surgical lung injury prediction model. *Anesthesiology.* 2011; 115:117–128. [PubMed: 21694510]
51. Kor DJ, Lingineni RK, Gajic O, et al. Predicting risk of postoperative lung injury in high-risk surgical patients: a multicenter cohort study. *Anesthesiology.* 2014; 120:1168–1181. A secondary analysis of a multicenter, prospective cohort investigation evaluating high-risk patients undergoing surgery to generate a refined prediction score to assess patients at risk for ARDS. The SLIP-2 score outperformed the original SLIP score in discrimination of at-risk patients for ARDS. [PubMed: 24755786]
52. Serpa Neto A, Simonis FD, Barbas CS, et al. Lung-protective ventilation with low tidal volumes and the occurrence of pulmonary complications in patients without acute respiratory distress syndrome: a systematic review and individual patient data analysis. *Crit Care Med.* 2015; 43:2155–2163. [PubMed: 26181219]
53. Gu WJ, Wang F, Liu JC. Effect of lung-protective ventilation with lower tidal volumes on clinical outcomes among patients undergoing surgery: a meta-analysis of randomized controlled trials. *CMAJ.* 2015; 187:E101–E109. Meta-analysis of randomized controlled trials to evaluate the effect of the ventilation strategy on postoperative outcomes. Patients who received ventilation with lower tidal volumes during surgery had a lower risk of lung injury and pulmonary infection than those given conventional ventilation with higher tidal volumes. [PubMed: 25512653]

54. Andrews PL, Shiber JR, Jaruga-Killeen E, et al. Early application of airway pressure release ventilation may reduce mortality in high-risk trauma patients: a systematic review of observational trauma ARDS literature. *J Trauma Acute Care Surg.* 2013; 75:635–641. [PubMed: 24064877]
55. Determann RM, Royakkers A, Wolthuis EK, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. *Critical care.* 2010; 14:R1. [PubMed: 20055989]
56. Severgnini P, Selmo G, Lanza C, et al. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. *Anesthesiology.* 2013; 118:1307–1321. [PubMed: 23542800]
57. ■. Nieman GF, Gatto LA, Bates JH, et al. Mechanical ventilation as a therapeutic tool to reduce ARDS incidence. *Chest.* 2015 Epub ahead of print A review about how protective ventilation strategies may help to prevent ARDS development.
58. Uchida T, Shirasawa M, Ware LB, et al. Receptor for advanced glycation end-products is a marker of type I cell injury in acute lung injury. *Am J Respir Crit Care Med.* 2006; 173:1008–1015. [PubMed: 16456142]
59. ■. Ware LB, Calfee CS. Biomarkers of ARDS: what's new? *Intensive Care Med.* 2015 Epub ahead of print An interesting review about current research in developing serum biomarkers for ARDS.
60. Muller MC, Tuinman PR, Vlaar AP, et al. Contribution of damage-associated molecular patterns to transfusion-related acute lung injury in cardiac surgery. *Blood Transfus.* 2014; 12:368–375. [PubMed: 24887223]
61. Jabaudon M, Blondonnet R, Roszyk L, et al. Soluble receptor for advanced glycation end-products predicts impaired alveolar fluid clearance in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2015; 192:191–199. [PubMed: 25932660]
62. Ware LB, Koyama T, Zhao Z, et al. Biomarkers of lung epithelial injury and inflammation distinguish severe sepsis patients with acute respiratory distress syndrome. *Critical care.* 2013; 17:R253. [PubMed: 24156650]