Acute respiratory distress syndrome

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Graduate Thesis

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Abbreviations

AECC:	American-European consensus conference
ALI:	acute lung injury
Ang:	angiopoietin
ARDS:	acute respiratory distress syndrome
ATP:	adenosine triphosphate
CPAP:	continuous positive airway pressure
CT:	computed tomography
ECMO:	extra corporeal membrane oxygenation
EVLW:	extra vascular lung water
HES:	hydroxyethyl starch
HFOV:	high frequency oscillatory ventilation
ICU:	intensive care unit
IL:	interleukin
MOF:	multi-organ failure
NMBA:	neuromuscular blocking agent
OSCAR:	high frequency oscillation in ARDS
OSCILLATE:	oscillation for acute respiratory distress syndrome treated early
PEEP:	positive end expiratory pressure
RBC:	red blood cell
SIRS:	systemic inflammatory response syndrome
TNF-a:	tumour necrosis factor alpha
VEGF:	vascular endothelial growth factor
VILI:	ventilator induced lung injury
vWF:	von willebrand factor

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Abstract

The Acute Respiratory Distress Syndrome (ARDS) is a well-known pathology in critical care medicine. ARDS can result from many pulmonary and non-pulmonary pathological insults. It is characterised by intractable hypoxia, diffuse alveolar damage, accumulation of protein rich alveolar fluid, and it can lead to multiple organ failure. The lack of objective clinical diagnostic tests and disease specific treatments are the reasons that ARDS remains a clinical diagnosis with high mortality. This challenge is met with multi-centre task forces assembled specifically to address current practices. Many current treatments and diagnostic algorithms, namely the Berlin definition of ARDS, have come from such cooperation. Indispensible in the treatment of ARDS is low volume mechanical ventilation with avoidance of excessive airway pressures, which is know as lung protective ventilation. Its role as well as the role of current supportive treatments including: fluid management, extracorporeal membrane oxygenation, sedation, neuromuscular blocking agents, and recruitment manoeuvres will be discussed.

Introduction

When the origins of the acute respiratory distress syndrome (ARDS) are discussed (1, 2), the study usually mentioned is that of Ashbaugh et al (3). The authors observed a similar clinical presentation between an adult population receiving respiratory therapy for an acute respiratory syndrome, with the known infant respiratory distress syndrome. This acute respiratory disorder was not only limited to the lungs in causing: hypoxemia, decreased compliance, and diffuse bilateral pulmonary infiltrates, but also existed as a multiple organ insult resulting in a high mortality of 58%. Diffuse alveolar damage is a key term regarding the pathophysiology of ARDS (4). Protein and inflammatory infiltrates enter the alveoli resulting in fluid draw, atelectasis, increased lung weight, decreased compliance, and eventually the syndrome culminates with a fibroproliferative phase, which can be concurrent with progressing multiple organ failure. The causes of ARDS are numerous and diverse. The initial pathological insult resulting in ARDS can be from both pulmonary and extra pulmonary causes, with direct pulmonary causes being more common (3, 5, 6). The key feature of an extra pulmonary cause is the systemic inflammatory response syndrome (SIRS). It is proposed that excessive activation of inflammatory and coagulation cascades, is essential in terms of lung injury and endothelial-alveolar dysfunction which contribute to the development of ARDS. These diverse pathologies create a clinical picture that is ARDS, which is defined by the Berlin criteria (7). The current criteria for diagnosis include the classic definition of acute lung injury (ALI) and ARDS as both ARDS. The removal of the categories of 200 mmHg

<PaO2/FiO2 <300 mmHg defining ALI allowed more comprehensive stratifying and better predictive value for mortality (7). This is critical as we see that early identification and treatment with protective ventilation of ARDS and at risk ARDS patients can improve clinical outcomes (8). The current mainstay of treatment is supportive care with lung protective mechanical ventilation (8-11). The clinical rationale for including classical ALI with ARDS will be discussed with regards to the essential initiation of early protective ventilation and ventilator settings themselves. Additionally, the current pathophysiological models of ARDS development will be discussed, along with current standards of care and developing treatments.

Pathophysiology of ARDS

Since the original description of ARDS (3), research into its pathophysiology using both clinical data and post mortem studies have furthered our understanding of the pathophysiology of ARDS. However, ARDS is a very diverse pathology that is an important clinical outcome to many pathological insults including: sepsis, shock, lung injury, polytrauma, and others insults which cause excessive activation of inflammation and coagulation cascades (11-13). The key feature of ARDS is damage to the alveolar epithelial and capillary endothelial cells, resulting in increased permeability. This cellular damage can result from direct pulmonary insults such as pneumonia, or from various extrapulmonary insults.

The Berlin definition of ARDS clinically classifies the disorder into mild

(200 mmHg < PaO2/FiO2 < 300mmHg), moderate (100 mmHg < PaO2/FiO2 > 200mmHg), and severe (PaO2/FiO2 <100 mmHg) categories (7). There must be additional requirements met in order for these ratios to be accurate in stratifying patients. Invasive mechanical ventilation must be used with positive end expiratory pressure (PEEP) of at least 5 cmH2O, with the exception of mild ARDS where continuous positive airway pressure (CPAP) can be used. Imaging should demonstrate opacities not explained by effusions, collapse or nodules (7, 14). The origin of lung oedema should not be from cardiac failure or from fluid overload (7, 14). These criteria should be established within 1 week of a known clinical insult or after new/rapidly worsening respiratory symptoms (7). While extensive and specific, the criteria outlined by the Berlin definition of ARDS allow for a better predictive validity for mortality, when compared with the older clinical criteria for ARDS, the American-European Consensus Conference (AECC) criteria (7).

While there is evidence that patients maintaining maximum lung fluid clearance have lower mortality and a shorter duration of mechanical ventilation(15), extra vascular lung water (EVLW) by itself is not a cause of ARDS, nor an independent predictor for mortality (15). This was a diagnostic criteria utilised before the Berlin definition was posed, which was subsequently removed as hydrostatic oedema is not a primary cause of respiratory failure (7). The key component in the pathology of ARDS appears to be capillary endothelial and alveolar epithelial damage, which allows protein rich fluid to accumulate in the alveoli with subsequent ability to clear such fluid being impaired (16).

Proteinaceous intra-alveolar fluid accumulation results in increased lung weight, atelectasis, impaired surfactant production, shunt, and further damage to the alveoli (15, 17). Decreased compliance, hypoxia and increased pressure required in mechanical ventilation are then to be expected. When a sufficient amount of lung parenchyma is involved, pulmonary hypertension also occurs which can potentially lead to right heart dysfunction. The progression of ARDS, beginning with diffuse alveolar damage, follows through three phases consisting of: exudation, fibroproliferation (proliferation) and resolution (4). The initial exudative phase corresponds to the Berlin criteria regarding deterioration in lung function with refractory hypoxemia (7, 13). A significant pulmonary or extrapulmonary pathology resulting in damage to the alveolar-capillary interface causes fluid, as well as cell material, proteins and inflammatory mediators to begin accumulating in alveolar spaces. The specific inflammatory mediators involved are numerous and remain a topic of investigation in order to further elucidate the pathophysiology of ARDS in addition to the search for diagnostic ARDS biomarkers (18-20). Migration of neutrophils to the alveoli also occurs, followed by histone release, an important cause of endothelial damage (21). After loss of epithelial cells and capillary endothelium, protein rich fluid fills the alveoli and in combination with cellular debris, cumulates in forming hyaline membranes (7, 22). The resultant clinical effects of the exudative phase are: decreasing effective lung surface area, decreasing compliance, and increase in shunt, which results in increased work of breathing. Injury to type 2 alveolar cells also results in decreased surfactant production (17), which further exacerbates the changes in

lung compliance, and represents a challenge for mechanical ventilation. Higher inspiratory pressures are then required to achieve alveolar opening. Overlapping with the exudative phase is the fibroproliferative phase. During this phase there is repopulation of type2 alveolar cells, fibroblast and myofibroblast proliferation as well as matrix deposition (23). The alveolar fluid resembles a more protein rich composition as oedema resolution occurs, due to type 2 alveolar basal Na/K ATPase dependent removal of fluid (15, 23). The proportion that the resulting fibrosis (and its potential recovery) owes to the damage of: pulmonary epithelium, capillary endothelium and degree of inflammatory processes during the ARDS is unclear and is also being discussed with respect to pulmonary and extra pulmonary causes (23). The majority of ARDS non-survivors show higher degrees of: capillary thrombosis, lung fibrosis and neovascularization (1). Approximately 60% of ARDS deaths occur within the first 14 days after diagnosis (11). However, the majority of ARDS deaths seem not to be attributed directly to the presence of a fibrotic lung or hypoxemia, but rather to multi organ failure (MOF) from a systemic inflammatory response syndrome (SIRS) due to the lung injury (2, 11).

Various extrapulmonary insults can result in ARDS, such as: trauma, pancreatitis, major trauma, burns, and haemorrhage (22, 24). These insults cause SIRS, which is associated with a systemic cytokine storm, cell damage and tissue injury. The aggressive inflammatory response causes injury to the pulmonary capillary endothelium, which initiates the acute phase of ARDS (23). As with the pulmonary insult, this endothelial damage also allows protein rich

oedema fluid accumulation within the alveoli. Concurrently, pro-inflammatory cytokines are released, and neutrophils are recruited, which continue to release toxic mediators, furthering free radical production and diffuse alveolar damage (13). In extraplumonary insults, it appears that ARDS is part of the multi organ damage associated with an excessive inflammatory response. The diagnosis of ARDS as well as findings on imaging for non-pulmonary insults, are as described for pulmonary insults (7).

Treatment

With the continuing exposure to ARDS in the ICU, physicians are continuing to advance current treatments. Also, new treatments and novel approaches are being currently researched. The existing standard treatments as well as possible future treatments for ARDS will be discussed.

Mechanical ventilation

Since the utilisation of mechanical ventilation is required to pose a diagnosis of ARDS as per the Berlin criteria (7), it is only fitting that it be used as the mainstay of treatment in ARDS. In ARDS the increased lung weight, decreased compliance and increased work of breathing leads to refractory hypoxia in the patient (7, 13). Supplemental oxygen and positive pressure ventilation combat this deficit. While mechanical ventilation is universally accepted as a life saving intervention it is not without it’s hazards. Over ventilation, namely using plateau pressures of greater than 30 cmH2O and high

tidal volumes have been recognised as precipitators of further lung injury (10, 25, 26). In ARDS, parenchyma elasticity is heterogeneous due to collapsed alveoli, increased EVLW, inflammation, and liquid plugs in conducting airways (10). There are three populations of alveoli in the lung model of ARDS (10): normal functioning alveoli, collapsed alveoli capable of opening with higher inspiratory pressures (recruitable), and collapsed non-recruitable alveoli. The “baby lung” concept describes the phenomenon of decreased available lung for ventilation (10) mainly due to lung heterogeneity. In this model, the normal functioning alveoli over distend during standard tidal volumes of 10-12 ml/kg in compensation of additional tidal volume from alveoli lost due to collapse (9). The resulting over stretch of the alveoli is referred to as volutrauma, and is the main cause of ventilator associated lung injury (9, 10, 27). Additionally, the repeated opening and closing of recruitable alveoli during ventilation, know as atelectrauma (28), results in further lung damage and increased lung heterogeneity (29). These two mechanisms of lung injury by mechanical ventilation are know collectively as ventilator induced lung injury (VILI) (28). VILI propagates further lung injury and alveolar collapse. This increased lung injury is hypothesised to increase neutrophil recruitment and inflammatory mediator release, which is known as biotrauma (9, 28). This is presumably one of the causes of MOF occurring in ARDS patients (28), as well as an explanation why mortality is higher in standard versus lung protective ventilation (9). In a major meta-analysis of twenty articles examining lung protective ventilation, 6-8 ml/kg were used as tidal volumes (9). Using low volume protective ventilation, in

conjunction with PEEP to increase alveoli recruitment, combats the refractory hypoxia seen in ARDS. The current accepted standard of therapy in mechanical ventilation for ARDS is using a target tidal volume of 6ml/kg and supplemental PEEP while maintaining plateau pressure <30cmH2O (25, 30, 31). However, with early studies applying these principles being conflicting (32, 33), further research and major centre trials were needed. One of the first major multi-centre studies on lung protective ventilation to show decrease in mortality was stopped after enrolling 861 patients as the difference in mortality from traditional ventilation was 31.0% vs. 39.8% P=0.007 (34). Results of lung protective ventilation have even warranted their use during non ARDS ventilation, such as in the operating theatre and in the general ICU population (9, 27, 30). There exists the potential for volutrauma during ventilation, therefore plateau pressure, comprised of PEEP and the pressure required to deliver tidal volumes, must be monitored, as using plateau pressures below 30 cmH2O is associated with a survival benefit (9). While mechanical ventilation is a potential cause for lung injury (27), low tidal volume ventilation in ARDS is an essential treatment protocol (7, 25).

High frequency oscillatory ventilation (HFOV) is ventilation using pressure oscillations to deliver tidal volumes with a relatively constant mean airway pressure (mPaw) at rates of 3-15 Hz (28). The result is small tidal volumes of 1-3 ml/kg around a “safe” area of the volume pressure curve (35), which theoretically avoids overdistension and atelectrauma. The use of low tidal volumes around a constant pressure is also intended to minimise the hemodynamic effects of mechanical ventilation. The device system used in adults is typically a membrane

diaphragm style, capable of oscillating to produce small volume displacements at high frequencies. Unlike in conventional ventilation, HFOV achieves adequate gas exchange with tidal volumes less than anatomic dead space. Gas transport is achieved by convective and diffusive mechanisms in the airways which causes gas mixing that is sufficient for exchange at the alveoli (36, 37). Although within normal physiology, tidal volume is more important than frequency in determining elimination of CO2, the ARDS lung is reliant more on frequency for CO2 elimination (35). With the potential of avoiding VILI in ARDS, HFOV became an attractive option in the ICU as an adjuvant to standard mechanical ventilation protocols. Initial studies showed potential promise in using HFOV, by demonstrating benefits to oxygenation and survival when compared to controls (38, 39). These studies however had small sample sizes and had utilised less than current ventilation protocols for their control groups. Two major studies set out to investigate the potential benefits of HFOV in ARDS treatment, which were the OSCILLATE trial (40) and the OSCAR trial (41). The OSCILLATE trial was a multi-centre randomised trial performed in 39 intensive care units in 5 countries. Regarding moderate to severe ARDS, they found that HFOV compared to lung protective ventilation was associated with no survival benefit, but rather an increase in mortality (47% to 35% in controls, CI 1.09-1.64, P=0.005) (40). The study was terminated early due to these preliminary findings. The OSCAR trial, performed in 12 university intensive care units, found that using 30 day all cause mortality as an end point, showed no significant difference between the HFOV and control (lung protective ventilation) groups (41). With the failure of studies to

effectively demonstrate a benefit for HFOV against current lung protective ventilation (38, 39), and with major randomised studies demonstrating either no benefit (41) or increased mortality (40), ARDS (and even non-ARDS) ventilation protocol remains as low tidal volume lung protective ventilation (9).

Extracorporeal Membrane Oxygenation

ECMO is a: venous-venous, arterial-venous (pumpless) or venous-arterial assist bypass device, which oxygenates and removes CO2 from blood and can be a partial cardiac assist device when used as venous-arterial oxygenation device (42). While requiring concomitant use of heparin to prevent clotting, these devices can deliver oxygen (3ml/kg/min) and remove CO2 (3-6ml/kg/min) to meet normal metabolic demands (42). The device can even serve as partial support, where its function is restricted to CO2 removal. With use of the ECMO system, expected patient complications include: bleeding, hemolysis, coagulation, clotting in the ECMO circuit, and thrombocytopenia (43). The use of ECMO has increased, notably during the H1N1 pandemic, however large randomised clinical trials investigating benefits to mortality are still lacking (44). Specifically with regards to ARDS, ECMO is being investigated as a means to further prevent VILI. While lung protective ventilation in ARDS constitutes using tidal volumes of 6ml/kg, there is evidence that even these volumes produce alveolar overdistension, which can be demonstrated on CT (45). A treatment approach currently being investigated with respect to ECMO is the use of a minimally invasive veno-venous (or arterial-venous pumpless) CO2 removal unit combined

with ultra-protective lung ventilation (<3ml/kg) to further avoid VILI (46, 47). Clinical outcomes were improved in ARDS patients when tidal volume was limited to <3ml/kg combined with pumpless arterial-venous ECMO to eliminate excessive carbon dioxide (46). While additional research is needed for the role of ECMO in ARDS, it is possible that it will become an adjuvant in the progression towards lower tidal volumes for the protection against VILI.

Lung Recruitment

While the use of low tidal volume ventilation with moderate PEEP ensuring plateau pressures less than 30 cmH2O is commonly used in ARDS, other ventilator strategies, physical manoeuvres, and even pharmacological treatments have been investigated to increase lung recruitment. Lung recruitment is the attempt to increase lung homogeneity and decrease VILI by opening recruitable alveoli and prevent their closure. The benefits to successful recruitment are: improved oxygenation, decreased VILI, and more accurate ventilation-perfusion matching (8). A number of methods exist in terms of recruitment manoeuvres. Short term increases in PEEP with higher lung volumes called “sighs” have been frequently employed (29). The results of this technique however, are not significant and result only in short term differences in oxygenation (29, 48). HFOV has also been used as a recruitment manoeuvre, yet it lacks any benefit in terms of improvements against mortality or clinical outcomes (40, 41). Various chest wall modification strategies to increase trans-pulmonary pressure have been investigated such as: abdominal decompression, regular pleural effusion

drainage, and allowing spontaneous breathing. However these methods have not gained sufficient promise to be utilised as standard treatments (7, 29). Prone positioning has been used to increase trans pulmonary pressure in the dorsal lung regions to create a regional PEEP effect in addition to improvements in ventilation-perfusion mismatching (29, 49, 50).

Prone positioning is being used in severe ARDS as a recruitment manoeuvre, and meta-analyses have already demonstrated improvements in oxygenation (51, 52). This improved oxygenation is attributed to increase in ventilation of perfused areas, therefore improving the ventilation-perfusion mismatch seen in ARDS (8). Additional benefits of prone positioning appear to be reduction in VILI. There is demonstrated reduction in lung stress-strain and lung concentration of pro-inflammatory cytokines (53), as well as in the amount of over distended lung areas, which can be demonstrated on CT (54). The reduction in stress-strain of the lung and the associated VILI is an important pathophysiological modification in severe ARDS. In addition to improved oxygenation and decreased amount of pro-inflammatory cytokines, which can affect systemic organ function, prone positioning may influence alveolar fluid clearance. The prevention of lung injury (53) spares alveolar epithelium which is associated with increased fluid clearance and better clinical outcomes (15). Taken together, these pathophysiological rationales of prone positioning support its clinical use in the treatment of ARDS. Additionally there is a demonstrated reduction in mortality using prone positioning in severe ARDS (49, 55), likely attributed to these and possibly other pathophysiological benefits.

Fluid Management

As with all ICU patients, fluid management is crucial. In ARDS however, it becomes more complex as there exists increased lung permeability, which results in alveolar fluid accumulation due to epithelial and endothelial damage (15). Additionally, extrapulmonary causes of ARDS often are due to sepsis, which globally increases vascular permeability (11-13). Intuitively, the approach to fluid management in ARDS would be to prevent over hydration to avoid excessive fluid leak, yet allow sufficient end organ perfusion. A major ARDS Network trial found that although no significant 60 day mortality difference was found between the fluid conservative and fluid liberal approaches, improved lung function and shorter duration of mechanical ventilation were seen in the fluid conservative group (56). Although extrapulmonary versus pulmonary causes for ARDS were not recorded, the researchers noted that fluid balance in the fluid liberal approach was similar to fluid balance in studies without strict fluid protocols, thus reflecting current fluid practices in the two ARDS causes (56). While there are pulmonary and extrapulmonary insults leading to ARDS, a large degree of patients have a sepsis related ARDS (57). This is important when considering the type and degree of fluid management in ARDS. The question of using crystalloids versus hydroxyethyl starch (HES) colloids has been extensively studied (50, 58, 59). A major review and meta analysis of literature concerning this question showed increased risk of renal replacement therapy, RBC transfusion, and severe adverse reactions when using HES in patients with sepsis (60). Initial fluid management in ARDS should follow surviving sepsis

guidelines (61, 62) without precipitating an excessive fluid balance as it is associated with poor outcomes (63). Additionally in ARDS, with or without sepsis, alveolar fluid clearance is impaired and increased EVLW is associated with poorer outcomes (15). Sepsis resulting in ARDS was associated with more severe impairment of alveolar fluid clearance, and this clearance was not affected by administration of catecholamines, dopamine or corticosteroids (15).

Pharmacological Treatments

Neuromuscular blocking agents (NMBA) have been employed in the treatment of ARDS. Most frequently they are used in conjunction with sedation to facilitate patient-ventilator synchrony (64). Asynchrony of ventilation can result in increased airway pressures, which is associated with barotrauma and VILI (65). When attempting to control increased airway pressures or increase lung recruitment with the prone position, NMBA's are used (66). A risk of NMBA use is muscle weakness and ventilator dependence. However, Papazian et al (67) found that early use of cistracurium in severe (<150 PaO2/FiO2) ARDS improved 90 day survival and increased time off the ventilator without increasing muscle weakness. Additionally, the study found no difference in gas exchange between treatment and placebo groups (67). It is proposed that the beneficial effects of NMBAs in this context is due to an anti-inflammatory property via their interaction with the nicotinic acetylcholine receptors, in addition to improving ventilator synchrony with the patient to avoid VILI (65). While lung protective effects have been seen with NMBAs, further studies are needed to confirm the benefits and

examine the mechanisms of their actions.

While corticosteroids are avoided in sepsis treatment guidelines, unless underlying shock is present (62), they have been under investigation for use in ARDS (68-70). Two mechanisms are proposed for the actions of corticosteroids based on their dosages. At low doses (<2.5mg/kg/day) they act at the level of the nucleus to increase anti-inflammatory mediator transcription, and inhibit pro-inflammatory mediators (71). High doses (>30mg/kg/day) show non-genomic effects at the cell surface to inhibit neutrophil degranulation (72, 73). In extensive examination of the literature concerning ARDS and corticosteroid use, low dosage shows potential lung function improvement and less time spent on mechanical ventilation, yet high dosage use is considered harmful (70). The impact of low doses on long term mortality is unclear (70). Some research indicates there is no benefit to its use (74), while other research indicates associations between corticosteroid use and the development of neuromyopathy (75, 76). Therefore further investigation is required before corticosteroids are widely accepted as an ARDS treatment.

Sedation use in ARDS facilitates ventilator-patient synchrony, patient comfort and somnolence, lower opioid use, and is necessary for mechanical ventilation. Its overuse can precipitate ventilator dependence, longer ICU stay and potential for brain dysfunction (77). Research is suggesting that regular sedation interruption versus continuous sedation can combat these side effects and lead to increases in ventilator free days (77, 78). An emerging sedative, dexmedetomidine, reduces duration of mechanical ventilation compared to

midazolam and propofol, and avoids propofol infusion syndrome (79). This a-2 adrenergic agonist causes central sedation and analgesia without significant respiratory depression (79). This lack of respiratory depression possibly aids in eventual ventilator weaning. It has been reported that use of dexmedetomidine is associated with more adverse events in comparison with midazolam or propofol (79).

Biomarkers

There are many proteins and inflammatory markers associated with ARDS. Notable proteins include: TNF-a, IL-6, IL-8, protein C, von Willebrand factor (vWF), and vascular endothelial growth factor (VEGF). The isolation of a specific biomarker for ARDS would provide an objective indication of disease status. There has been extensive research and review in the search for ARDS biomarkers, notably with cytokines (19, 20, 47, 80). The interest in using inflammatory cytokines as biomarkers arose from correlations between IL-1b, TNF-a, and ARDS mortality (20, 81). The challenge with using cytokines as ARDS specific biomarkers is the heterogeneity of ARDS causes. This is demonstrated by the lack of IL-1b and TNF-a in trauma patients with ARDS (82, 83). IL-6 additionally, correlates with ARDS development in diverse ICU patients but shows inconsistent association with trauma associated ARDS (82, 83). With the multitude of cytokines associated with ARDS, it appears there are differences in their expression regarding different causes of ARDS. Their overlapping expression also compounds the possibility of using them as a disease specific

biomarker.

Endothelial proteins Ang-1 and Ang-2 are markers of endothelial health and dysfunction respectively. Ang-2's has been studied in sepsis as a therapeutic target and disease marker (84, 85). Levels of Ang-2 or ratio of Ang-2/Ang-1 correlates with mortality in sepsis and also represents endothelial health (85). Increased Ang-2 levels have been demonstrated in ARDS (18, 86, 87), and show a correlation with mortality (18). Additionally, trauma patients have shown correlations between Ang-2 levels and the development of ARDS (88). With endothelial dysfunction being a key feature of ARDS, further research with Ang-2 could show promise in identifying patients who are at risk of ARDS and in predicting mortality of patients with ARDS.

The challenge with obtaining an ARDS specific biomarker is that ARDS represents a syndrome rather than a single disease entity. Thus finding a specific biomarker to predict ARDS development, severity, and mortality remains a daunting task. It is possible however that a combination of markers could be used to aid in predicting ARDS outcome.

Conclusion

ARDS remains an important cause of mortality in the ICU. Lung protective ventilation is the mainstay of treatment, along with supportive measures. ECMO, prone positioning and pharmaceuticals are adjuvants to mechanical ventilation. There is no unique treatment protocol for ARDS from pulmonary versus extra-pulmonary causes. Objective tests are still under investigation and ARDS remains a clinical diagnosis, supported by imaging. Additional multi-centre clinical trials are needed to expand on treatment protocols in order to decrease the mortality from ARDS.

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Bibliography

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