Journal of
Anesthesia & Intensive Care Medicine
ISSN: 2474-7653

Juniper Publishers
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Research Article
Volume 7 Issue 2 - July 2018
DOI: 10.19080/JAICM.2018.07.555707

J Anest & Inten Care Med

Recent Issues in ARDS

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Submission: May 29, 2018; **Published:** July 16, 2018

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Definition

Depending on Berlin definition, ARDS is an acute form of diffuse lung injury detected in patients with a predisposing risk factor, fulfilling these criteria: (1) onset within 1 week of a known clinical insult or new/deteriorating respiratory symptoms; (2) presence of bilateral opacities on chest X-ray, not fully clarified by effusion, lobar/lung collapse, or nodules; (3) diagnosis of respiratory failure not fully interpreted by cardiac failure or fluid overload; (4) presence of hypoxemia, as demarcated by a specific threshold of the PaO_2/FiO_2 ratio measured with a minimum necessity of PEEP ≥ 5 cm H_2O, thus classifying three classes of severity: mild (PaO_2/FiO_2 >200 mm Hg ≤ 300 mm Hg), moderate (PaO_2/FiO_2>100 mm Hg ≤ 200 mm Hg) or severe (PaO_2/FiO_2 ≤ 100 mm Hg) [1].

Diagnosis

Common etiologies for ARDS are: pneumonia, sepsis, trauma, pancreatitis, inhalation injury, gastric content aspiration, non-cardiogenic shock, burns, drug overdose, and drowning and acute lung injury subsequent to massive transfusions. Certainly, a promising outcome of ARDS patients can be obtained with adequate treatment of the original cause. Unquestionably, pneumonia still remains the principal cause of ARDS, therefore the first step is to rapidly recognize the pathogen responsible for the infection, and microbiological evaluation for any potential pathogens designates the first diagnostic effort [2]. Consequently the initial assessment should incorporate: blood cultures, urinary antigen testing for *Legionella pneumophila* and *Streptococcus pneumoniae,* serologic tests for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, and microbial sampling of the lung, preferably comprehended with a fiberoptic BAL.

BAL cytology, CT scan and immunologic examinations should be accomplished, spotting for less common etiologies especially viral infections that played an important role in increased frequency of ARDS in recent years. Ultimately, if neither CT scan nor BAL cytology help the diagnosis, open lung biopsy should be achieved to recognize the underlying trigger reason [3-5]. A CT chest scan is usually done to better realize the underlying pathophysiology and the possible presence of hidden diagnosis; characteristic morphological forms are: consolidated regions, ground glass areas and normally aerated regions. Consolidated regions are typically restricted to the dependent areas of the lung. Furthermore, CT scan is useful in evaluating the extent of lung recruitability. The presence of non-inflated areas determines a major expansion of the neighboring lung regions, causing an increase in the local pressure and thus acting as a "stress raiser".

Classically, pulmonary ARDS present a comparable amount of consolidated and ground glass areas, while extrapulmonary ARDS have a greater amount of ground glass areas. CT scan may also be helpful in describing the distribution of lung opacities and, in some cases; it may permit the detection of an unsuspected pneumothorax or help to identify the ARDS cause [6]. Transthoracic ultrasound has a vital role in diagnosis and management of ARDS. The crucial finding in patients with ARDS is a B-line artifact, defined as the presence of a distinct vertical hyperechoic reverberation artifact that arises from the pleural line and extend to the edge of screen. The finding of three or more B-lines in one intercostal space is considered abnormal and is termed B-pattern. A non-homogeneous scattering of B-pattern, C (consolidative) pattern, pleural line abnormalities and absence of pleural effusion are characteristic of ARDS and distinguish it from cardiogenic pulmonary edema. The systematic use of thoracic ultrasonography as a tool for bedside appraisal of ARDS evolution has been suggested by some authors [7].

Treatment

Noninvasive ventilation, High flow nasal cannula and oxygen therapy

To our knowledge, only one randomized study compared high flow nasal cannula, NIV and oxygen therapy in acute respiratory failure, the results illustrated that there is no difference between the three groups with reverence to the intubation rate, while in the high flow nasal cannula group the mortality in intensive care unit was lower [8].

Invasive mechanical ventilation

Mechanical ventilation denotes a supportive therapy able to guarantee adequate gas exchange, providing both rises in PaO_2

and CO_2 elimination, while reducing the work of breathing. The effect of mechanical ventilation on oxygenation is dual: first, it permits the titration of FiO_2; secondly, it offers, during the inspiratory phase, enough positive pressure to ensure the opening of collapsed pulmonary units. However, without the application of a suitable level of Positive End Expiratory Pressure (PEEP), the same pulmonary units will collapse again during the expiratory stage [9].

Really, a completely "safe" ventilatory strategy does not exist, and the support must be tailored to each single patient, constructed on hemodynamics, gas argument, lung recruitability and respiratory mechanics [10]. It had been suggested that the application of high PEEP levels, while opening the collapsed alveoli and decreasing the intrapulmonary shunt, might decrease the repetitive alveolar opening and closing during the whole respiratory cycle [11]. However, when two different large randomized controlled studies were completed to compare ARDS patients treated with low versus high levels of PEEP, the outcomes did not reveal any benefit of a high PEEP strategy [12,13]. Several procedures exist to recruit the lung, such as the sigh (a high tidal volume intermittently delivered during ventilation), the extended sigh (a stepwise increase of PEEP or both PEEP and plateau pressure) and the sustained inflation (a static increase in airway pressure applied for 20-40 seconds). The main goal, regardless of the technique used, is to apply a high transpulmonary pressure for an adequate time, so to cause the reinflation of the closed pulmonary units. While these procedures are capable, without major disadvantages, to improve oxygenation for a variable period of time, however their use has not revealed to lead to a significant decrease in mortality [14].

Lung recruitment

In patients with ARDS, a variable degree of lung recruitability was demonstrated, ranging from 0% to 70% of the total lung weight as assessed by lung CT-scan. Pulmonary CT-scan is the gold standard for the measurement of lung recruitability, although it necessitates the transport of the patient outside the ICU and radiation exposure. As a good substitute, lung ultrasound proved dependable option in estimating lung recruitability at the bedside [15,16]. Different forms of recruitment procedures, such as sustained inflation, intermittent sighs and stepwise increase in inspiratory pressure, have been proposed. Definitely, the optimal procedure has not yet been demarcated. Independently of the specific maneuver applied, oxygenation increases for a certain period of time without major side effects; but, recruitment maneuvers alone were not linked to a reduction in the mortality [14].

PEEP selection

The choice of the ideal level of PEEP is an issue tough to resolve: if PEEP is too low some part of recruitable tissue will collapse, whereas excessive PEEP creates dead space and tissue stretch. The idea behind the application of PEEP has altered over time: while in the sixties it was considered as a tool to improve oxygenation, it is now regarded as an important element to avoid the repetitive alveolar opening and closing during the respiratory cycle, so that it touched a prominent position in the framework of lung protective ventilatory strategy [17]. Really, the main query is how to titrate PEEP on individual patients. Numerous tactics have been suggested to set PEEP; the most commonly used is titration based on a PEEP/FiO_2 table [18].

Alternative method is constructed on respiratory mechanics, with the aim of maintaining airway pressure under a safe limit (26-28 cm H_2O), through stepwise escalation of PEEP while maintaining a constant tidal volume [19]. Some authors revealed better compliance and oxygenation when PEEP was applied according to an absolute level of end-expiratory transpulmonary pressure between 0 and 10 cm H_2O [20]. Other authors used the tidal variation in esophageal pressure, rather than its absolute value, to assess the total end-inspiratory transpulmonary pressure, then used as an indicator of lung stress [21]. To reduce the risk of Ventilator Induced Injury (VILI); some authors recommend to asses ARDS severity by ventilating the patient at PEEP 5 cm H_2O in pure oxygen, and in moderate-to-severe ARDS, lung recruitability should be calculated by lung CT scan or ultrasound, and high PEEP levels >15 cm H_2O should be realistic. In addition, to avoid lung overstress, transpulmonary pressure should be measured while concurrently titrating PEEP and tidal volume [22].

Tidal volume setting

The ARMA trial confirmed the advantage of using a low tidal volume of 6 mL/kg (predicted body weight), as compared to the high tidal volume of 12 mL/kg in achievement of 22% reduction in mortality [23]. Another meta-analysis confirmed those judgments, illustrating a significant reduction in 28-day mortality in patients subjected to the so-called "lung-protective ventilation" and the conclusion of this study is that the use of a large tidal volume increases the risk of developing ARDS, while the exposure to high tidal volumes in patients with well-known ARDS increases mortality [24].

Recently, Amato et al. [25] reported that the airway driving pressure was the aspect most associated with the outcome: a higher mortality was only found when higher plateau pressures were observed in patients with higher driving pressures. Likewise, the protective effects of higher PEEP was only perceived when this was accompanied with a decreased driving pressures, with a cutoff for increased mortality at a driving pressure of 15 cm H_2O [25]. However, the driving pressure has restrictions, the main being that transpulmonary pressure, and not airway pressure, is the relevant distending pressure for the lung. This is important as the chest wall has been as unpredictably changed in ARDS. Definitely, the measurement of functional residual capacity, as an index of the baby lung size, appears more physiologically appropriate, and its use may open the route to new studies that may further improve tidal volume setting [26].

A recent paper exposed how airway driving pressure can detect lung overstress with acceptable accuracy patients with

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ARDS, as those with higher airway driving pressure group had a significantly higher lung stress, respiratory system and lung elastance as compared to those with lower airway driving pressure [27]. In the past the selection of pressure-controlled versus volume-controlled ventilation was considered relevant for patient outcome, two recent meta-analysis were incapable to detect any significant difference in mortality, risk of barotrauma, cardiac output, gas exchange or work of breathing [28].

Oxygen and carbon dioxide objective

The actual recommendation is a conservative oxygenation strategy with an arterial oxygen saturation goal between 88% and 95% in patients getting invasive mechanical ventilation. Definitely, the use of a low tidal volume, with the target to decrease the risk of VILI, may lead to the development of hypercapnia. However, arterial carbon dioxide levels up to 70 mm Hg with a pH of 7.20 were found to be harmless [29] in the absence of elevated intracranial pressure or right sided heart failure. The basis of a more liberal CO_2 management (permissive hypercapnia) deceits in the recognized positive effects of hypercapnic acidosis on arterial and tissue oxygenation: the potentiation of hypoxic pulmonary vasoconstriction, the inhibition of airway tone, the increase in cardiac output, the anti-inflammatory effect and the rightward shift in the oxygen-hemoglobin dissociation curve [30].

Prone positioning

The practice and indications of prone positioning in patients with ARDS has been altered over time. While decades ago this procedure was only performed to improve arterial oxygenation in life-threatening acute respiratory failure [31]. It is currently clear that prone positioning allows for a more homogeneous distribution of stress and strain, thus helps to protect lung against the VILI [32]. The greatest important values of prone positioning effect are: a better ventilation/perfusion matching with a subsequent improvement in CO_2 clearance, a more homogenous distribution of ventilation with a decrease of VILI and a recruitment of dorsal regions through the redistribution of lung densities [33]. Therefore, prone positioning should be performed to all patients with severe ARDS, especially in the acute phase, because of the higher likelihood to recruit lung parenchyma [34].

The Proning Severe ARDS Patients (PROSEVA) trial demonstrated a greater extubation success and a significant decrease in 28-day mortality in the prone positioning-group (16% vs. 32%). Undeniably, the simultaneous use of prone positioning and Neuromuscular Blocking Agents (NMBAs) could apply a synergistic effect on oxygenation and reducing the period of mechanical ventilation, finally improving the ultimate outcome. The limited absolute contraindications to prone positioning are: pregnancy, hemodynamic instability, open abdomen treatment and unstable fractures [35].

The philosophy of Extracorporeal Membrane Oxygenation (ECMO) for the treatment of ARDS is the application of an artificial lung that may provide an adequate blood oxygenation and CO_2 elimination, allowing reducing mechanical ventilation. A randomized trial (CESAR study) of patients with ARDS referred to an ECMO center showed a higher 6-months survival rate (63% vs. 47%) and no difference in quality of life and spirometric parameters compared to patients treated with conventional mechanical ventilation [36]. In spite of these positive data, the CESAR trial has been criticized for its design; therefore, currently, is not possible to conclude for a advantage of ECMO with respect to conventional mechanical ventilation [37].

Pharmacologic Interventions

Neuromuscular blocking agents (NMBAs)

The aim is to improve patient-ventilator synchrony and to decrease the oxygen consumption related to respiratory muscle activity. A further effect of NMBAs is the reduction of the negative escalation in pleural pressure appreciated during spontaneous breathing, with the likely subsequent reduction of stress and strain applied to the lung [34]. In contrast, NMBA usage may induce diaphragmatic dysfunction or ICU-acquired weakness. It has been shown that patients with severe ARDS receiving an early, short-course of NMBAs presented lower mortality, reduced period of mechanical ventilation and less events of barotrauma [35].

Inhaled vasodilators

Despite the vasodilator action utilized by nitric oxide on the pulmonary vasculature, leading to an improved ventilation/perfusion matching, its use in ARDS patients is highly controversial, as no clear mortality benefit could be demonstrated. Furthermore, its use was associated with important cost-safety concerns and an increase in the incidence of renal failure [38].

Corticosteroids

The basis for steroid use in ARDS is the major role of the inflammatory response in the pathogenesis of ARDS. Based on these impressions, several trials investigated corticosteroids use [39,40], however with marked controversial results. Meduri et al. [39] in their study performed in the early phase of ARDS illustrated a reduction in ICU mortality rate; however, these findings could not be detected in other studies [40,41]. Some authors suggested the presence of steroid-responsive and steroid-independent inflammatory axes during the course of ARDS, and that MicroRNA (miRNA) and corticosteroids may have similar but relatively independent mechanisms that modulate inflammation. The increased expression of miRNA, independent of corticosteroid therapy, may suggest a role in steroid-independent mechanisms that contribute to the resolution of inflammation, thus potentially explaining the different response to corticosteroid therapy seen in different patient cohorts [42].

Conclusion

ARDS still remains a syndrome with a raised global incidence, and with an attributable mortality extending from 40% to 60%. Its definition has been reviewed several times, the last in Berlin, 2011, to permit for a better precision of the clinical diagnosis. A

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quick documentation of the underlying etiology is mandatory, and the use of a systematic methodology to diagnosis may help the clinicians. Lung CT is an important radiological option for the diagnosis of extra-pulmonary causes of ARDS and for the assessment of lung recruitability with subsequent choice of ventilator setting. Ultrasonography has an important role in the bedside appraisal of lung parenchyma beside left and right ventricular function. It has the advantages of bed side availability, lack of ionizing radiation, low price and safe repeated examinations.

The supportive treatment for ARDS should be directed to sustain the vital functions, to improve and ensure an adequate gas exchange, while reducing the probability to cause VILI. Irrespective of the mode of mechanical ventilation, lung recruitability should be evaluated before applying the PEEP value, and an inspiratory O_2 fraction should be chosen to target an arterial saturation between 88% and 95%. Lung volume and transpulmonary pressure monitoring are very vital to adjust the ventilator settings and to avoid lung overstress, while maintaining a lung-protective strategy. Finally, the use of prone positioning and NMBAs should always be considered, at least in the most severe cases.

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DOI: 10.19080/JAICM.2018.07.555707

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