Therapeutic principles in the acute respiratory distress syndrome – the concept of "protective mechanical ventilation"

Principii terapeutice în sindromul de detresă respiratorie acută – conceptul de "ventilație mecanică protectivă"

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Abstract

The adult respiratory distress syndrome (ARDS) represents a very severe form of acute respiratory failure which is underlain by lesional (noncardiogenic) lung edema and is defined by a series of clinical, imaging, hemodynamic and oxygenation criteria. Most cases need rapidly established invasive ventilatory support, preferably, in intensive care units with expertise in the care of these patients. Even with the appropriate therapy, the prognosis is unfavourable, and mortality is high. Protective mechanical ventilation is a complex concept based on the existence of multiple areas with different degrees of lung damage; it is meant to maintain acceptable gaseous exchanges (permissive hypoxemia and hypercapnia) by reducing the risk of trauma through mechanical ventilation. The protective mechanical ventilation strategies reduce complications and mortality. The alveolar recruitment manoeuvres and techniques for keeping the recruited areas open by using positive end-expiratory pressure (PEEP) and the prone-position ventilation (ventral decubitus) are extremely important and with proved results. Other methods addressing the gaseous exchanges may improve oxygenation but not also mortality. General supporting measures and complications prevention are part of the complex therapeutic approach of these cases.

Keywords: ***acute respiratory distress syndrome, protective mechanical ventilation, alveolar recruitment manoeuvres, prone-position, PEEP***

Rezumat

Sindromul de detresă respiratorie a adultului (SDRA) este o formă de insuficiență respiratorie acută de o gravitate extremă care are ca substrat un edem pulmonar lezional (non-cardiogen) și este definit de un ansamblu de criterii clinice, imagistice, hemodinamice și de oxigenare. Cele mai multe cazuri necesită suport ventilator invaziv rapid instituit, de preferință în secții de terapie intensivă cu experiență în îngrijirea acestor pacienți. Chiar și cu terapie adecvată, prognosticul este infaust, iar mortalitatea este ridicată. Ventilația mecanică protectivă este un concept complex care are la bază existența mai multor zone cu grade diferite de afectare în plămân; aceasta are drept obiectiv menținerea unor schimburi gazoase acceptabile (hipoxemie și hipercapnie permisive) cu reducerea riscului de traumă prin ventilație mecanică. Strategiile de ventilație protectivă reduc complicațiile și mortalitatea. Manevrele de recrutare alveolară și de menținere deschisă a zonelor recrutate prin utilizarea de PEEP, alături de ventilația în prone-position (decubit ventral) sunt extrem de importante și cu rezultate dovedite. Alte metode de îmbunătățire a schimburilor gazoase pot ameliora oxigenarea, dar nu și mortalitatea. Măsurile suportive generale și profilaxia complicațiilor fac parte din abordul complex terapeutic al acestor cazuri.

Cuvinte-cheie: ***sindromul de detresă respiratorie acută, ventilație mecanică protectivă, manevre de recrutare alveolară, prone-position, PEEP***

Introduction

The acute respiratory distress syndrome (ARDS) is an extremely serious and life-threatening medical condition, characterised by acute respiratory failure, hypoxemia resistant to the administration of oxygen, pulmonary compliance compromised due to lesional lung edema and marked inflammation of both lungs. The majority of patients would die without mechanical ventilation; even with appropriate therapy, the prognosis is unfavourable and mortality is high.

The diagnosis of ARDS is based on a series of clinical, imaging, hemodynamic and oxygenation criteria. There are no clinical or laboratory signs specific to the diagnosis of this entity.

Although the subject aroused the interest of many researchers (over 20,000 articles on this topic in PubMed), there are few efficient treatments for ARDS besides the protective mechanical ventilation[1].

ARDS definition

The first description of this syndrome dates back to 1967 and belongs to Ashbaugh et al.[2]; they reported 12 cases "very similar to the respiratory distress syndrome of the newborn" who needed mechanical ventilation and the use of positive end-expiratory pressure (PEEP). They had high mortality (7 of 12 cases), and autopsy revealed heavy lungs, diffuse alveolar atelectasis, interstitial and alveolar edema, as well as formation of hyaline mem-

Table 1 Berlin definition of ARDS versus the definition of AECC[5]

	AECC definition	Berlin definition
Time factor	Acute onset	Within **one week** from a potentially generating clinical insult -or from the occurrence/ worsening of respiratory symptoms.
ALI category	All patients with (PaO_2/FiO_2<300 mmHg)	It no longer exists; it becomes synonymous with mild ARDS.
Oxygenation	$PaO_2/FiO_2 \leq 200$ mmHg (regardless of PEEP)	**Mild:** 200 < $PaO_2/FiO_2 \leq 300$ mmHg with PEEP/CPAP ≥5 cmH_2O **Moderate:** 100 < $PaO_2/FiO_2 \leq 200$ mmHg with PEEP ≥5 cmH_2O **Severe:** $PaO_2/FiO_2 \leq 100$ mmHg with PEEP≥5 cmH_2O
Thoracic X-ray	Bilateral lung infiltrates	**Thoracic imaging (X-ray or CT):** Bilateral opacities, insufficiently explained by the fluid discharges, lobe/lung atelectasis, nodules.
PAWP	PAWP≤18 mmHg or without clinical evidence for the increase in the pressure in the left atrium	**Origin of edema:** Respiratory failure insufficiently supported by heart failure or fluid overloading. Objective measurements are necessary (e.g., echocardiography) in order to exclude hydrostatic edema, when risk factors are missing.

Abbreviations: PaO_2 – partial pressure of oxygen in arterial blood; FiO2 – fraction of oxygen in inhaled air; ALI – acute lung injury; ARDS – acute respiratory distress syndrome; PEEP – positive end-expiratory pressure; CPAP – continuous positive airway pressure; PAWP – Pulmonary artery wedge pressure

branes. This entity was initially called "the adult respiratory distress syndrome".

Subsequently, there were multiple reviews of the definition or attempts to quantify the degree of physiological damage for a more precise diagnosis and a more accurate estimate of the prognosis of the patients with ARDS. Thus, Murray[3] proposed a "score of pulmonary injury" (Lung Injury Score; LIS), abandoned in 1994 after turning to a new definition of ARDS, drawn up by AECC (American-European Consensus Conference Committee)[4], which was used for almost 20 years.

The term "adult" was replaced by "acute", and the syndrome was defined as hypoxemia with acute onset ($PaO_2/FiO_2 \leq 200$ mmHg), X-ray visible bilateral infiltrates similar to lung edema, but without signs of pressure increase in the left atrium. The same consensus conference defined a new term: acute lung injury (ALI), which had the same diagnosis criteria, but with a larger spectrum of impairment of oxygenation ($PaO_2/FiO_2 \leq 300$ mmHg), this contains the cases of ARDS, but also some with less severe oxygenation damage (PaO_2/FiO_2 201-300 mmHg).

In time, this definition of AECC proved unsatisfactory from several perspectives. Starting from that, but also to reflect the new information and the experience gathered in time, a panel of international experts was formed, representing the main medical societies in the field (European Society of Intensive Care Medicine, American Thoracic Society, Society of Critical Care Medicine), that drew up in 2011 the Berlin definition[5] of ARDS, thus beginning to addresss to the uncovered or unclear aspects of the previous definition (Table 1).

Mortality is proportional to the severity of ARDS, the average value is 24% for mild ARDS, 32% for moderate ARDS and 45% for severe ARDS (95% CI)[5]. The Berlin definition of ARDS has validity in the superior prediction of mortality compared to AECC, with an area under the curve AUROC of 0.577 vs. 0.536. The categories mild, moderate, severe of ARDS correlate well with the duration of mechanical ventilation, with the lung weight estimated by CT and with the intrapulmonary shunt fraction.

Etiology

ARDS is the result of an aggression upon the alveolo-capillary membrane which leads to its increased permeability, with secondary alveolar and interstitial edema.

The causes of ARDS are multiple and diverse. Some occur through direct lung injury ("direct" causes), others are located outside the lung, but through a systemic inflammation involving multiple pro-inflammatory mediators, they finally lead to lung injury which triggers ARDS ("indirect" causes). The list of the conditions potentially causing ARDS is presented in Table 2.

In approximately 20% of the ARDS cases, a condition causing this syndrome cannot be identified.

Still, not all patients exposed to the situations above progress towards ARDS. There are a number of factors which seem to increase the risk of developing ARDS in the presence of triggering conditions: old age, female gender (for trauma), smoking[7], alcohol consumption, high severity of the underlying disease (assessed with a high APACHE score).

An important role is played by the natural immunity which may efficiently contribute to the removal of the pathogens, but it may amplify lung lesions and inflammation at this level.

Treatment

Despite the progress made in better understanding the pathophysiological mechanisms involved in ARDS, there are very few therapies which proved their efficiency in limiting the morbidity and mortality of this extremely severe medical condition: early and correct treatment of the cause of ARDS, protective mechanical ventilation (see the definition of this term below), maintaining a negative hydric balance, the ventral decubitus of the patient – "prone position", the use of neuromuscular blockers.

Table 2 The most common causes of ARDS[6]

	DIRECT LUNG INJURY ("direct" causes)	INDIRECT LUNG INJURY ("indirect" causes)
FREQUENT CAUSES	Pneumonia (viral, bacterial, fungal) Aspiration of gastric content	Sepsis Severe trauma
LESS COMMON CAUSES	Pulmonary contusion Injury through inhalation (smoke, oxygen, ammonia, hydrocarbons etc.) Pulmonary embolism (fat, amniotic) Choking Lung irradiation Reperfusion pulmonary edema	Acute pancreatitis Drug overdose Cardiopulmonary bypass Massive transfusions Extensive burns Severe uremia
SPECIAL, RARE CASES	Miliary tuberculosis Cryptogenic organizing pneumonia Acute eosinophilic pneumonia	

The aggressive management of the triggering condition is thus doubled by supportive therapy; placing the patient within an intensive care unit experienced in this field is ideal, and there is evidence this measure influences the survival[8]. A very important aspect is the early recognition and the correct treatment of the complications which may occur: multiple organ failure, nosocomial pneumonia, deep venous thrombosis, gastrointestinal hemorrhage etc[9].

1. Mechanical ventilation

Most patients with ARDS need invasive mechanical ventilation. A minority (those with mild forms of ARDS, previously defined as acute pulmonary injury) may be treated with non-invasive ventilation, but only in intensive care units with experience in the field and under careful monitoring; this may be administered *via* oro-nasal mask or full facial mask, or through high flow nasal cannulas (deliver oxygen in a flow of up to 50 l/min, humidified and heated).

The difficulties of mechanical ventilation in ARDS start from the heterogeneous distribution of the areas affected in the lung, which makes the relatively unaffected areas to receive disproportionately large volumes of air at each breath, with the supradistension of these territories (*volutrauma*) resulting in very large pressures in these regions (*barotrauma*).

Three different areas can be described in the lung with ARDS (Figure 1): posterior areas of atelectasis, intermediary areas which may be recruited with appropriate ventilation and anterior aerated areas with normal compliance. The lung in its assembly behaves like that of a baby ("baby lung"), and thus the tidal volume used in these patients should be proportionally reduced.

Volutrauma together with the *atelectrauma* (cyclic opening and closing of the affected units in the lung) generate the release of proinflammatory mediators (*biotrauma*), and barotrauma may lead to complications such as pneumothorax, pneumomediastinum, subcutaneous emphysema etc. For the risk reduction of these complications of mechanical ventilation, neuromuscular blockers are used for severe ARDS and for limited periods of time.

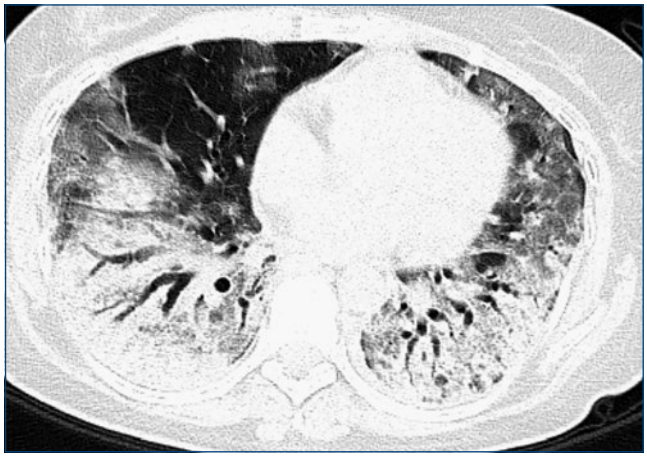

Figure 1. *CT image of an ARDS patient which proves the inequality of the lung damage, the lesions being predominantly in the posterior areas*

Protective mechanical ventilation (whose parameters are defined in Table 3) has a positive influence upon morbidity, mortality and the rate of complications of the mechanical ventilation[10,11,12].

It thus leads to oxygenation under the thresholds considered optimal in other conditions (*"permissive hypoxemia")* and an incomplete removal of CO_2 from blood (*"permissive hypercapnia").* In practice, increases of $PaCO_2$ are allowed as long as oxygenation is acceptable and pH is maintained >7.2[9].

ARDS Network[11] compared the old strategy (ventilation with tidal volume of 12 ml/kg body weight) with this protective mechanical ventilation strategy (the use of a tidal volume of 6 ml/kg body weight) and proved a reduction in mortality from 40% to 31%, with more days without mechanical ventilation and without failure in other organs in the second group.

Still, not all patients may be ventilated using the parameters mentioned previously. Thus, the ones with cerebral edema cannot be ventilated with that "permissive hypercapnia", which might worsen the edema, and other patients cannot withstand small tidal volumes due to the severe damage of the oxygenation[13].

Table 3 Protective mechanical ventilation protocol in ARDS[11]

Ventilation method	Assisted-controlled mode in pressure or volume
Tidal volume	≤ 6 ml/kg bodyweight
Plateau pressure	≤ 30 cm H_2O
Respiratory rate	6-35/min, to reach an arterial pH≥7.3
Inspiratory flow, I:E ratio	Flow adjusted for reaching I:E of 1:1 – 1:3
Oxygenation objective	PaO_2 ≥ 55 mmHg or 88<SaO_2<95%
FiO_2/PEEP	0.3/5; 0.4/5; 0.4/8; 0.5/8; 0.5-0.7/10-14; 0.8-0.9/14; 0.9/16-18; 1/18-24 (PEEP max 34 cm H_2O)
Withdrawal method	With the pressure support mode FiO_2/PEEP ≤ 0.4/8

I:E = inhalation/exhalation ratio; FiO_2 = fraction of inspired oxygen; PEEP = positive end-expiratory pressure

It should be tried to maintain a FiO_2 value as small as possible (0.4-0.65) in order to prevent toxicity and the effects of oxygen *per se*, but this may be achieved by using PEEP, as it results from the gradual increase algorithm of the FiO_2/PEEP ratio in Table 5.

Another important concept in addition to the one of protective ventilation is that of *opening the lung* through alveolar recruitment and of *keeping it open* through the application of PEEP[14]. This concept refers to the reduction of the poorly ventilated territories which may be recruited and the prevention of atelectrauma and biotrauma by keeping them open. Several techniques are used for recruitment: the application of high PEEP (35-40 cm H_2O) for 30-40 seconds, the intermittent use of tidal volume, or the prolongation of sigh[11]. The potential secondary effects of the recruitment manoeuvres are low blood pressure and barotrauma.

Others strategies for the improvement of gaseous exchanges in ARDS

Ventilation in prone position: it allows the alveolar recruitment in the posterior areas, with a more uniform distribution of the tidal volume, with an oxygenation improvement in 70% of the cases, allowing the reduction in PEEP and FiO_2[15]. The latest studies and meta-analyses confirm a significant mortality reduction, by over 15%, in the patients ventilated in prone-position both at 28 days and at 90 days[16,17], this becoming a definitive recommendation during mechanical ventilation in patients with ARDS.

Inverse Ratio Ventilation: recruits alveoli by extending the inspiratory time (I/E=2/1 or 3/1).

Other ventilation methods: Airway Pressure Release Ventilation (APRV), BiPAP, proportional assist ventilation (PAV), High frequency ventilation (HFV), high frequency oscillation (HFO) – these are methods which allow, each through a different mechanism, the improvement of the gaseous exchanges avoiding alveolar supradistension.

Inhaling nitric oxide during mechanical ventilation: it acts as a vasodilator, reduces the average lung pressure and reduces the intrapulmonary shunt. Still, the data in some studies which investigated the impact of using NO in patients with ARDS did not prove the beneficial effects upon mortality and the duration of mechanical ventilation[18].

Performing of ***extracorporeal gas exchanges***: it should be considered in patients with severe forms of ARDS, hypoxemia resistant to the ventilation and recruitment strategies mentioned – in order to prevent oxygen toxicity in high FiO_2 and volu- and barotrauma. Either ECMO (extracorporeal membrane oxygenation), or $ECCO_2R$ (extracorporeal carbon dioxide removal) may be performed. There is the supposition that extracorporeal oxygenation by leaving the lung at rest may improve the lung repair process, but this has not yet been validated by the clinical studies. The CESAR study demonstrated the survival benefit for patients transferred to a reference centre for ECMO, especially for patients with ARDS within the flu A (H1N1/09)[19,20]. The indications of using ECMO are: patients with potentially reversible respiratory failure with the ratio PaO_2/FiO_2<80 despite using a high PEEP (15-20 cm H_2O) for at least 6 hours or hypercapnia with acidemia (pH<7.15) or plateau pressure>35-45 cm H_2O.

Figure 2 presents a synthesis of the methods of therapeutic intervention in ARDS according to its severity[21].

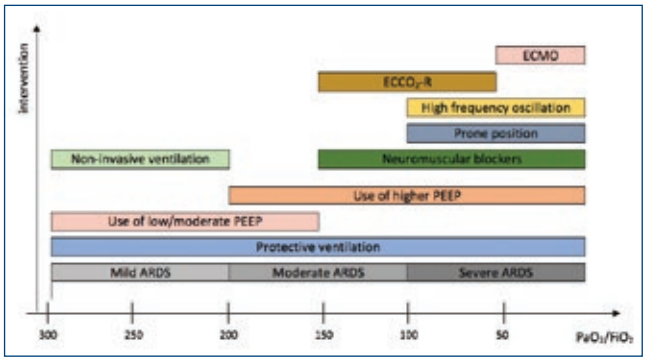

Figure 2. *Therapeutic methods in ARDS according to severity (adapted from Froese AB et al.[21])*

2. Other therapeutic non-ventilatory strategies

Fluid management: maintaining a negative hydric balance (monitoring *via* Swan-Ganz or central venous catheter, monitoring diuresis ± diuretics/hemodialysis) seems to bring benefits on oxygenation, the score of lung injury, the number of days of mechanical ventilation and cognitive function after ARDS, without an impact upon mortality[22].

Nutritional support: it is recommended that nutritional support is applied after 48-72 hours of mechanical ventilation, preferably *via* the enteral path, with low carbohydrate food, rich in fat, including anti-inflammatory agents, antioxidants and vasodilators (eicosapentaenoic and linoleic acids). This type of nutrition brings benefits on survival and oxygenation[23].

Corticosteroids have been extensively used in ARDS, especially in patients with persistent infiltrates, fever, hypoxemia difficult to improve and in extended ARDS. Large doses of i.v. methylprednisolone offer an immediate benefit (improvement of oxygenation and hemodynamics), but without an impact on mortality and with the known secondary effects of corticotherapy[24]. Consequently, it is not recommended to use corticosteroids as a routine in patients with extended ARDS.

Prevention of complications: prophylaxis of deep vein thrombosis, of stress ulcer, early mobilization, minimisation of sedation, prevention and care of bedsores, measures for the prevention of ventilator associated pneumonia.

Other therapies: the inhalatory administration of synthetic surfactant, i.v. anti-endotoxin immunoglobulins, simvastatin, ibuprofen, ß2 agonists, prostaglandin E, inhibitors of neutrophilic elastase, pentoxifylline, acyclovir, GM-CSF etc. proved to have no benefit in ARDS[25].

Future therapies: *gene therapy* for supporting the migration of Na^+ through the alveolar-arterial barrier or for the production of IL-10, IP-10, IL-12, TGF-ß1, the use of *mesenchymal stem cells*[1].

Conclusions

ARDS (with its different degrees of severity) is a **medical condition of extreme severity** which may complicate the evolution of a series of medical and surgical diseases, sometimes located outside the lung.

It is recommended that patients with ARDS be admitted as **soon** as possible in **intensive care units with experience** in the treatment of such cases.

The quick identification of the **triggering cause** and its prompt and correct treatment have a definite influence upon the evolution of the case with ARDS.

Most patients need **invasive mechanical ventilation**. The protective mechanical ventilation strategies reduce complications and mortality.

Protective mechanical ventilation is a complex concept based on the identification of multiple areas with different degrees of lung damage; trying to maintain acceptable gaseous exchanges (**permissive hypoxemia and hypercapnia**) by reducing the risk of trauma through mechanical ventilation (volutrauma, barotrauma, atelectrauma, biotrauma).

Other methods for the improvement of gaseous exchanges may improve oxygenation, but not also mortality.

General supporting measures and the prophylaxis of complications are part of the complex therapeutic approach of these cases, with impact upon the final result.

Although the **mortality** rate continues to decrease with the new ventilatory strategies, it continues to be **high**, and many times the survivors have a poor quality of life. ■

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