In this review, fundamental concepts are gathered on the use of mechanical ventilation (MV) in children with acute respiratory distress syndrome (ARDS) and refractory hypoxemia. Protective MV and recruitment potential (RP) concepts are discussed, and ventilatory options and/or maneuvers intended to optimize non-ventilated lung tissue –alveolar recruitment maneuver (ARM), positive end-expiratory pressure (PEEP) titration, high-frequency oscillatory ventilation (HFOV) and airway pressure release ventilation (APRV)– or aimed to correct ventilation/perfusion (V/Q) mismatch –use of the prone position– are examined, and as the sole pharmacological measure, the use of neuromuscular blockers is discussed. In clinical practice, the protective MV concept implies individualized PEEP and tidal volume (V_t) adjustments. The use of alveolar recruitment maneuvers and PEEP down-titration can improve pulmonary function in ARDS patients. Early implementation of HFOV should be considered in MV-failure scenarios. Early and prolonged use of the prone position can increase gas exchange while waiting for better control of the cause that prompted the use of MV.

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A search was carried out in PubMed, looking for publications on ventilatory strategies used for refractory hypoxemia in the setting of ARDS, using the following key terms: “acute respiratory distress syndrome”, “protective mechanical ventilation”, “ventilator-induced lung injury”, “ventilatory strategies”, “alveolar recruitment maneuver”, and “refractory hypoxemia”. Those that, according to the authors’ opinion were the more relevant to be known by the pediatric intensive care specialist, were selected. The present update is not a systematic review on the subject.

**Fundamentals of protective mechanical ventilatory therapy in acute respiratory distress syndrome**

Acute respiratory distress syndrome is a serious and complex condition, devastating in nature and with high mortality in both adult (40%) and children (26%) populations, which lacks effective drug therapy and specific treatment. It is characterized for being an entity with diffuse pulmonary involvement, inflammatory in nature, with increased permeability in the alveolar capillary membrane and varying degrees of interstitial edema, with gravitational collapse of the airway space and alveolar instability caused by dysfunction of the surfactant system, alveolar occupation by protein deposition and presence of detritus. Clinically, it is characterized by the presence of hypoxemia caused by decreased pulmonary distensibility, increased pulmonary shunt and increased physiological dead space.

Currently, refractory hypoxemia is an uncommon cause of death: 10-19% of ARDS adult patients. However, in the largest study performed on routine protective MV use in children, refractory hypoxemia was found to be the cause of death in 26.3% of patients.

There is still no standard definition for it, in terms of a predetermined PaO2 value under specific FiO2 and PEEP for a given period. Most reports use PaO2 < 70 mm Hg with FiO2 of 0.8-1 and PEEP > 10 cm H2O over a period longer than 12 to 24 h.

Recently, the ARDS definition has been reviewed, and it has been classified according to the PaO2/FiO2 ratio for an established PEEP, with three mutually-exclusive hypoxemia categories, with severe ARDS established as a PaO2/FiO2 ratio < 100 mm Hg with PEEP ≥ 5 cm H2O (Berlin definition).
The reason for this selection of the severe ARDS criterion is based on the fact that many studies have demonstrated a worse prognosis in the lowest oxygenation quartile regardless of the employed ventilatory strategy. In 2012, the PEDALIEN (Pediatric Acute Lung Injury: Epidemiology and Natural history) trial corroborated that mortality is doubled in patients with PaO₂/FiO₂ < 100 mm Hg at the onset of ARDS compared with those with values > 100 mm Hg (33.7 vs. 16.7%).

The use of MV remains the cornerstone of therapy, and its purpose is to search for a ventilatory strategy that allows for reasonable gas exchange to be obtained while being able to minimize injury produced by the ventilator.

Evidence recommends using tidal volume between 6-8 ml/kg ideal weight with Pplat ≤ 30 cm H₂O. The use of high PEEP levels has not been shown to reduce mortality; however, it has improved important secondary goals.

Currently, it can be claimed that ventilatory therapy influences the patient’s evolution, either negatively (worsening the condition or delaying the cure) or positively if a protective ventilatory strategy is employed. To sum up, a protecting MV involves non-ventilated tissue recruitment using recruiting maneuvers (see below), preventing cyclic alveolar collapse and avoiding excessive alveolar distension. For the latter, it is important for the driving pressure to be lower than 15 cm H₂O.

Theories on the causes of reduced aeration capability

Mechanisms limiting the pulmonary volume to receive the delivered Vₕ (baby lung) are interstitial edema and alveolar flooding. In the first, a decrease in functional residual capacity (FRC) occurs due to the loss of gas caused by the superimposed hydrostatic gradient of lung tissue (“sponge lung”) that upon insufflation is characterized for incorporating new alveolar units, which improves FRC and the development of alveolar recruitment (see below). In the second mechanism, FRC is not modified by the use of PEEP, since the alveoli are occupied by proteins and detritus, which prevents their collapse. In these cases, during insufflation, the volume is distributed towards normally-ventilated zones, thus causing alveolar overdistension.

Both mechanisms reveal mechanical stress on a lung with reduced aeration capability.

Lung recruitment

The open lung approach (OLA) is a strategy aimed at the re-expansion of collapsed lung tissue by using high PEEP levels in order to prevent subsequent derecruitment. Its benefits are: arterial oxygenation improvement due to intrapulmonary shunt fraction and pulmonary distensibility reduction by a shift of the curve’s slope to a higher efficiency point and prevention of alveolar unit’s cyclic opening/collapse at each ventilatory cycle.

Given the underlying pathophysiology, the ideal patient to apply the ARM is that with early stage ARDS (prior to the start of fibroproliferation). Although, theoretically, extrapulmonary ARDS-patients might have better response to these maneuvers (larger gravitational fluid collapse component), according to our experience, the response is similar in children with serious primary ARDS, with early implementation being more relevant. Relative contraindications are presence of disease predisposing to air leak syndromes (v.gr., congenital lobar emphysema) and hemodynamic instability (uncorrected hypovolemia).

Alveolar recruitment maneuvers

Alveolar recruitment maneuvers have been recommended as adjunctive measures to protective ventilation strategies, since ventilator-induced lung injury (VILI) can be relieved by opening and maintaining open those cyclically collapsing units (atelectrauma). Even with strict adherence to pressure or volume limitation during the use of MV, up to a third of patients experience alveolar overdistension at the end of inspiration. This phenomenon occurs mainly in patients with high proportion of non-aerated tissue, presumably because the Vₕ is delivered into a smaller aerated compartment. By recruiting non-aerated tissue, damage by overdistension can be attenuated due to a largest volume of aerated lung available for the Vₕ to distribute more homogeneously.

In experimental animal models, the use of ARM has been shown not to cause epithelial damage to the same extent as the use of harmful ventilation. There are different protocols for its implementation and several methods have been described to recruit the collapsed lung, although superiority of one method over another has not been demonstrated. A common component of these protocols is the deliberate use of higher positive pressure (transpulmonary pressure increase [Pₜₚ]) for limited time. Though not always effective, these maneuvers usually improve oxygenation and respiratory mechanics. After their implementation, an adequate PEEP should be used, and it is advisable for the PEEP to be titrated downwards, maintaining the benefit of...
an open lung. Using a higher PEEP after the ARM has been shown to influence the duration of its effect 19.

The moment at which the maneuver is performed also seems to play a role in effect duration, since the longer the ARDS time of evolution, the lower the obtained beneficial effect 20,21.

In a recent systematic review 22, the most commonly used method was sustained insufflation. With this maneuver (40 cm H2O for 30 s) the highest recruitment has been shown to occur in the first 10 s, subsequently developing hemodynamic compromise 23; however, this hemodynamic deterioration can be attenuated through thorough assessment and eventual correction of the pre-charge. The use of maneuvers with 10-15 cm H

2O driving pressure should be considered, rather than continuous positive airway pressure (CPAP), due to better hemodynamic tolerance. It should be kept in mind that under tissue dysoxia conditions, the delivery of oxygen (DO2) has to be improved, rather than reaching a particular PaO2 value (Fig. 2).

However, significant controversy continues to exist on its efficiency 24,25 and deleterious side effects 26-29. In addition, these maneuvers have a diagnostic role, since they allow for the recruitment potential (RP) to be determined; there are different modalities to estimate the potential of response to ARM, such as the use of ultrasound 30, electrical impedance tomography 31 or thoracic computed tomography 32.

In children, evidence on their possible usefulness is still lacking and, therefore, its routine use can not be recommended. In a recent work 33, in patients with severe hypoxemia, 90% effectiveness was demonstrated with the use of sequential ARM. Its effectiveness was assessed with regard to a change of at least 25% in dynamical distensibility (Cdyn) or PaO2/FiO2. This improvement in the lung function was maintained in two thirds of the patients at 24 h. An inverse correlation was found between baseline Cdyn or PaO2/FiO2 values and their change after the maneuver, suggesting that patients with severe ARDS experience higher response. Figure 3 shows the recruitment and PEEP titration maneuver used in our unit.

In summary, we can point out that the ARM must be performed early in the course of ARDS, in a progressive/sequential way for better hemodynamic tolerance and in pressure control ventilatory modality, which has demonstrated superiority over CPAP. A more prolonged effect is obtained on the time in alveolar stability if pressure control and PEEP down-titration are employed. The benefit is marginal with the use of pressures higher than 40 cm H2O and/or time longer than 2 min. No benefit has been demonstrated of its use with regard to improving the ARDS patient prognosis and, in patients with severe hypoxemia, its use should be considered on an individual basis 22.

Positive end-expiratory pressure titration

The use of an adequate PEEP is an essential element in protective pulmonary ventilation, since it allows for the lung to remain open and limits the VILI, this way turning into the mainstay of the open lung concept. PEEP is an end-expiratory phenomenon and, therefore, it is effective only to maintain open those alveoli that were previously recruited during the insufflation. Furthermore, the use of PEEP results in an improvement in oxygenation secondary to increased functional residual capacity, extrapulmonary vascular water redistribution and improvement of the V/Q ratio 34.

Determination of the optimal PEEP while maintaining protective ventilation has varied over time and has been the subject of multiple studies. Several methods have been proposed, such as the use of the FiO2-PEEP table 35, PEEP gradual increase using a Pplat < 30 cm H2O 36, the pressure-volume curve to determine the lower inflection point, on which the PEEP is established (+2-3 cm H2O) 37, stress-index measurement using the pressure-time curve under constant flux 38, esophageal pressure measurement to estimate intrapleural pressure 39 and step-wise PEEP down-titration until derecruitment occurs, apparent by a fall in PaO2 and distensibility 40,41. Although each one of these strategies shows limitations and there is no consensus yet on which the best method is, PEEP down-titration is the
one used by our group and the method we will refer to subsequently.

Dynamic distensibility can be a useful indicator in the search for the optimal PEEP. Its assessment is carried out downwards: initially, the $C_{\text{dy}}$ will increase with PEEP gradual reductions, which will indicate relief for overdistended areas of the lung; then, it will reach a plateau, without an increase being observed when decreasing of the PEEP is continued. If the level of delivered PEEP continues to be reduced, the $C_{\text{dy}}$ will start to decrease, which will indicate an initial collapse of alveolar units that can not be kept open, this way identifying the “lower inflection point”. Optimal PEEP must be adjusted at least 2 cm H$_2$O above this inflection point, selecting the most safe and efficacious individual PEEP/VT combination.

If there is the desire to titrate a PEEP, the RP of the patient has to mandatorily be considered. When the PEEP is increased, two situations can develop: a) the expiratory reserve volume (ERV) will not increase, thus reflecting low or no RP (consolidation $>$ collapse), or b) an ERV increase, indicating high RP. In the first case, the PEEP increase will cause non-collapsed alveoli overdistension, which results in $V_t$ being able to overcome the critical $P_{\text{TR}}$ of the sick lung, thus generating stress and strain ($V_t$ $>$ baby lung). In the second scenario, the same $V_t$ can be distributed into a higher number of alveolar units, with a resulting $P_{\text{TR}}$ reduction and strain limitation ($V_t$ $<$ baby lung). This way, theoretically, high levels of PEEP should be reserved only to patients with high RP, otherwise, and moderate levels.

**High-frequency oscillatory ventilation**

High-frequency oscillatory ventilation was described by JH Emerson in 1952 and clinically developed early in the 70’s by Lukenheimer42,43. HFOV can be described as a pressure-controlled ventilatory modality that delivers small tidal volumes. The physiological rationale behind this modality is based on maintaining a high end-expiratory pulmonary level (open lung) by applying mean airway pressure (MAP) on a safety zone located between the pressure-volume curve inflection points, where oscillatory pressure amplitude ($\Delta P$) overlaps at supraphysiologic pressure ranging from 3 to 15 Hz. A $V_t$ is thus generated close to the anatomical dead space (1-3 ml/kg). It shows an active expiratory phase, which prevents air entrapment and facilitates CO$_2$ sweeping.

Oxygenation is achieved by increasing the used MAP and FiO$_2$. Then, according to the oxygenation

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**Figure 3. Alveolar recruitment and PEEP down-titration assay protocol.** This strategy is carried out under the pressure control modality. It is started with 10 cm H$_2$O PEEP maintaining distension pressure steady at 15 cm H$_2$O. The recruitment maneuver is performed sequentially by increasing the PEEP 5 cm H$_2$O every 2 min until a 25 cm H$_2$O PEEP is reached. PEEP titration is based on gasometry and lung mechanics. RM: recruitment maneuver (modified from Cruces et al.33).
goal. MAP is progressively increased while allowing for a parallel decrease of the delivered FiO2 levels. If necessary, an ARM can be performed by applying 40 cm H2O over 40 s (oscillator in the off position).

Alveolar ventilation (VCO2) is a function of oscillation frequency (f) and squared tidal volume (VCO2 = f x VT2)44,45; consequently, most CO2 elimination is achieved mainly by increasing the VT. By widening the oscillation magnitude (ΔP), VT will be increased (positive correlation), which, additionally, depends on the size of the endotracheal tube (ETT) and the employed f. Maximal ventilation occurs with the highest VT delivered and the lowest recommended frequency, since its reduction allows for wider oscillation of the piston (increase in VT), which enables for higher CO2 sweeping.

As for the moment to start the HFOV, there is no consensus on a MAP value on which it should be used. Nevertheless, in the most important series it is close to 20 cm H2O, with a progressive increase of the oxygenation index (OI = 100 x MAP x FiO2/PaO2)46. The use of HFOV should be considered in case of:
- Conventional MV failure, either when oxygenation goals are not achieved without exceeding safe Pplat and VT levels (OI > 16) or when the extent of hypercapnia is out of tolerable range47. We must keep in mind that HFOV should be started as soon as possible.
- Air leak syndrome difficult to manage in MV.

Recently, the results of two important multi-center works conducted in adult populations have been published: the British OSCAR48 and the Canadian OSCIL-LATE49. In the first, no difference in observed mortality was demonstrated for ARDS patients treated with HFOV or standard MV (41%), whereas in the second, the use of HFOV was found to be associated with higher mortality (47%) than a standard ventilatory strategy with low VT and high PEEP levels (35%). The presence of refractory hypoxemia was higher in the control group than in the group of patients HFOV-connected; nevertheless, the number of post-hypoxemia deaths was similar in both groups.

Recently, a work by Gupta et al.50 reported an observational study in children, with ages ranging from 1 month to 18 years, comparing the use of HFOV versus CMV. Mechanical ventilation time duration, ICU length of stay and mortality (8 vs. 18%) favored widely the use of standard MV. In view of these results, which suggest a worse prognosis for the use of HFOV, further studies are required in the pediatric population to define the exact role of HFOV in the treatment of acute hypoxemic respiratory failure.

Airway pressure release ventilation

It is a relatively new mode described two decades ago51,52. This modality is cycled by time and limited by pressure. It is characterized by a high level of continuous airway positive pressure (Phigh), where periodic releases of this pressure are applied at a lower level of airway pressure (Plow). The distinctive feature of APRV is the presence of a constantly active expiratory valve, which enables spontaneous breathing anytime in the cycle and in a time-cycle-independent manner. Different ratios between Phigh and Plow have been employed (Fig. 4). Periodical releases provide with a back-up VT that, together with respiratory rate, enable ventilation, whereas the Phigh period results in lung recruitment and effective oxygenation. Caution should be used with potential overdistension caused by spontaneous breathing (negative pleural pressure) during the Phigh stage, as well as also with derecruitment (atelectrauma) that can occur if the Plow period duration is not short enough. It should be noted that, in the absence of spontaneous breathing, the APRV is functionally identical to the pressure control modality with inverted relationship. Conversely, since spontaneous breathing is maintained, profound sedation and muscle paralysis requirements are lower.

Other benefit of maintaining spontaneous breathing during the APRV, especially in ARDS patients, is the result of diaphragmatic contraction that occurs, where recruitment is observed in the juxta-diaphragmatic-dependent pulmonary zone, thus improving the V/Q ratio and oxygenation and potentially reducing the likelihood of VILI53-55.

Airway pressure release ventilation is an alternative approach to OLA for the patient with ARDS. APRV can resemble a continuous recruitment maneuver (high pressure in 80-95% of the cycle).

Data in pediatric populations are very limited and they are mainly case reports56,57. It is an interesting ventilatory modality with a number of theoretical benefits such as protective ventilation and hypothetical advantages over the HFOV.

Recently, in an experimental animal model, the use of early-start APRV was compared with low-volume ventilation (6 ml/kg), demonstrating greater benefits with regard to permeability biomarkers and alveolar stability, as well as gravimetric and histological indicators of ARDS development for its use58.

Finally, in spite of its demonstrated physiological beneficial effects, there is a need for studies to be designed in order to assess its potential benefit in clinical practice and, hence, to elucidate its exact role in the ventilatory management of the ARDS patient.
Pronation

Currently, this maneuver is widely used. Its benefit is based on gravitational forces inversion with pleural pressure decrease in dorsal regions, which allows for a more homogeneous distribution of the V/Q ratio to be achieved, coincident with the pulmonary vertical axis (Fig. 5). Improvements in pulmonary mechanics and gas exchange physiological variables (systemic oxygenation improvement) have been demonstrated; however, there are no data demonstrating its actual impact on global mortality, which limits it to a routine use.

Generally, in children it is an easy-to-perform, practical and safe therapeutic maneuver. The timing component in its use is crucial, and its greatest benefits are obtained when applied early in an edematous and atelectasic lung, i.e., with higher RP.

Currently, there are no clinical guidelines recommending an optimal duration for pronation, although prolongation of this intervention does not seem to be beneficial. Patients not responding at 2 h, do it after 12 h, with a response rate that changes from 58 to 100%. In our casuistry, 72 h constitutes an effective and safe “dose” (Fig. 5).

A prospective study in adults describes a “time-dependent” gas exchange, intrapulmonary shunt and extravascular lung water improvement with 18 h in the prone position. This way, the adequate prone position “dose” for ARDS patients that is able to maintain the gasometric and mechanical advantage when the patient is repositioned to the supine position, remains to be established.

Gattinoni et al. analyzed the four major studies conducted in adult patients, and concluded that the prone position decreases mortality in cases of severe hypoxemia, providing its use is within the first 72 h and for a prolonged period (16 h/day).

Recently, Guérin et al. reported a decrease in mortality in ARDS patients when the prone position was used for prolonged periods (73% of the time on MV). No greater benefit was observed in patients with more severe hypoxemia.

Neuromuscular blockade

Recent data confirm the beneficial effect of the use of neuromuscular blockers, for no longer than 48 h, during severe ARDS early stage and in the most hypoxemic patients. Their use is based on facilitating the patient’s ventilation and controlling patient-ventilator asynchrony, in addition to their effect on protective MV by a reduction of biotrauma, which can be supported by the smaller number of organ failures in groups receiving neuromuscular blockade.

The decision on their use must be assessed considering the risks, such as prolonged neuromuscular weakness, especially with concurrent use of steroids or in patients with hyperglycemia. It is important highlighting that protective MV can be achieved in most patients without the use of neuromuscular blockers, with their use being reserved to a reduced group of patients ((severe ARDS) and for limited time.)
Neuromuscular blockade

Acute respiratory distress syndrome is a common complication of several critical diseases. It is characterized by a severe-natured lung diffuse inflammation, with the development of high-permeability pulmonary edema. MV is initially the necessary vital support, and the use of protective MV with low $V_T$ is the current standard of care; however, lung injury can be generated ocassionally when non-protective ventilation is used in response to the development of refractory hypoxemia and ultimately contribute to mortality of patients.

Upon the occurrence of refractory hypoxemia, the physician must consider a number of ventilatory strategies aimed to increase the exchange surface and this way correcting the hypoxemia, including alveolar recruitment maneuvers, PEEP titration, HFOV, APRV and prone position. Regardless of the lung protection ventilatory strategies to be used, these should be titrated according to the individual respiratory pathophysiology of the patient.

Although these strategies have been shown to correct hypoxemia, their impact on vital prognosis has not yet been proven. Future studies are needed to elucidate the efficacy of these therapies in the prognosis of patients with severe ARDS and refractory hypoxemia.

References

Ventilation strategies in the child with severe hypoxemic respiratory failure

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