

Ventilation strategies in the child with severe hypoxemic respiratory failure

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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. (Gac Med Mex. 2015;151:69-77)

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Introduction

The development of severe hypoxemia constitutes an important complication in ARDS, especially since extracorporeal support therapies are not readily available for many hospital centers. If mechanical ventilation (MV) implementation fails to reverse hypoxemia, generally employed initial therapeutic measures are: increasing the fraction of inspired oxygen (FiO_2) and the PEEP, in addition to sedation optimization and/or eventually adding the use of myorelaxants.

Every acute respiratory failure that under a lung-protective strategy persistently maintains an arterial oxygen partial pressure (PaO_2)/ FiO_2 ratio < 100 mmHg, or failure to maintain a plateau pressure (P_{plat}) < 30 cm H_2O , can be classified as refractory hypoxemia¹. Upon this scenario, conventional ventilatory therapy needs to be optimized by incorporating new treatment strategies and/or ventilatory maneuvers to the available algorithms, which act on a number of pathophysiological aspects. These treatment strategies are applied according to the severity of ARDS, which is useful for the clinician, since allows for management of the patient to be carried out in a simplified and protocolized way (Fig. 1). The purpose of this review is to analyze the mechanisms that cause the decrease of aeration volume, as well as to describe the fundamentals of the main ventilatory modalities proposed in the past few years to be used in the severely hypoxemic child.

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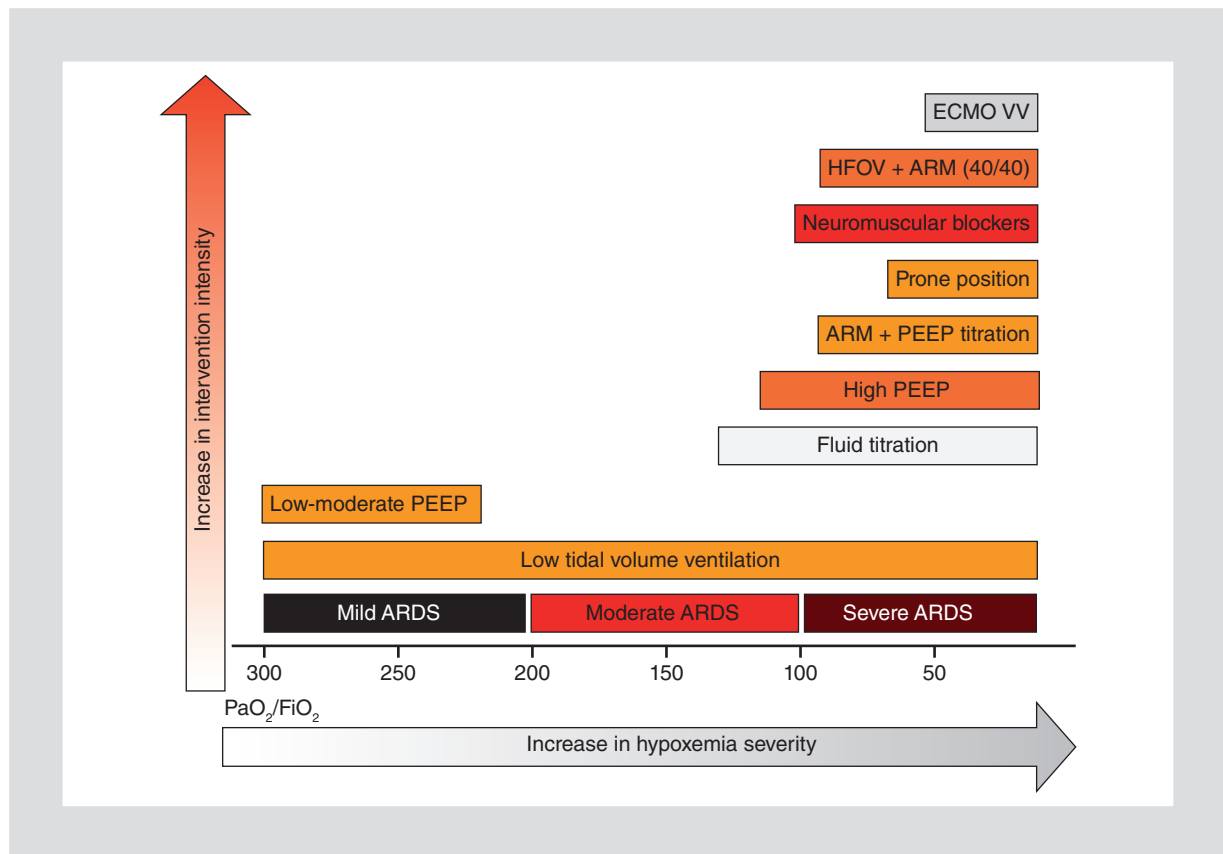


Figure 1. Ventilatory, pharmacological and extracorporeal support strategies according to ARDS severity (modified from <http://www.esicm.org>). ECMO VV: extracorporeal membrane oxygenation veno-venous.

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 condition², devastating in nature and with high mortality in both adult (40%)³ and children (26%)⁴ 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 ede-

ma, with gravitational collapse of the airway space and alveolar unstability caused by dysfunction of the surfactant system, alveolar occupation by protein deposition and presence of detritus^{5,6}. 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 patients³. 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 patients⁴.

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 h⁷.

Recently, the ARDS definition has been reviewed², and it has been classified according to the PaO₂/FiO₂ ratio for an established PEEP, with three mutually-excluding 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^{3,8,9}.

In 2012, the PEDALIEN (Pediatric Acute Lung Injury: Epidemiology and Natural history) trial corroborated that mortality is doubled in patients with $\text{PaO}_2/\text{FiO}_2 < 100$ mm Hg at the onset of ARDS compared with those with values > 100 mm Hg (33.7 vs. 16.7%)⁴.

The use of MV remains the cornerstone of therapy¹⁰, 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 ventilator¹¹.

Evidence recommends using tidal volume between 6-8 ml/kg ideal weight with $\text{Pplat} \leq 30$ cm H_2O . The use of high PEEP levels has not been shown to reduce mortality; however, it has improved important secondary goals¹².

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 H_2O .

Theories on the causes of reduced aeration capability

Mechanisms limiting the pulmonary volume to receive the delivered V_T (baby lung) are interstitial edema and alveolar flooding^{13,14}. 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)¹⁵.

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 inspiration¹⁶. This phenomenon occurs mainly in patients with high proportion of non-aerated tissue, presumably because the V_T 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 V_T 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 ventilation¹⁷.

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 [P_{TP}]) for limited time¹⁸. 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

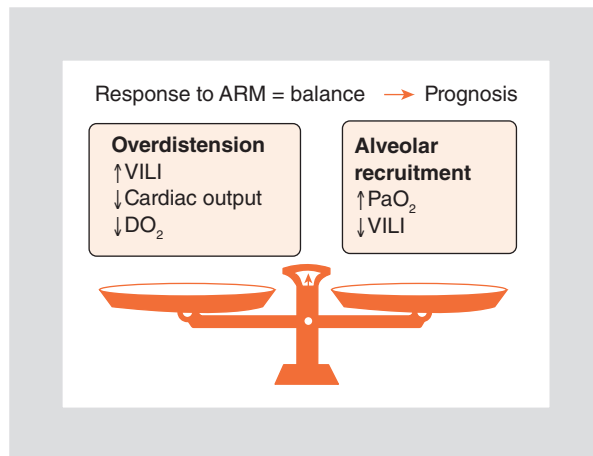


Figure 2. Balance between risks (left) and benefits (right) of the ARM. Individual response to ARM will depend on this balance and will have a potential effect on the prognosis of the patient.

an open lung. Using a higher PEEP after the ARM has been shown to influence the duration of its effect¹⁹.

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 review²², 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 compromise²³; 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 H₂O 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 effects²⁶⁻²⁹. 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 ultrasound³⁰, electrical impedance tomography³¹ or thoracic computed tomography³².

In children, evidence on their possible usefulness is still lacking and, therefore, its routine use can not be recommended. In a recent work³³, 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 (C_{dyn}) 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 C_{dyn} 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 basis²².

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 ratio³⁴.

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^{9,35}, PEEP gradual increase using a Pplat < 30 cm H₂O³⁶, 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 flux³⁸, esophageal pressure measurement to estimate intrapleural pressure³⁹ 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

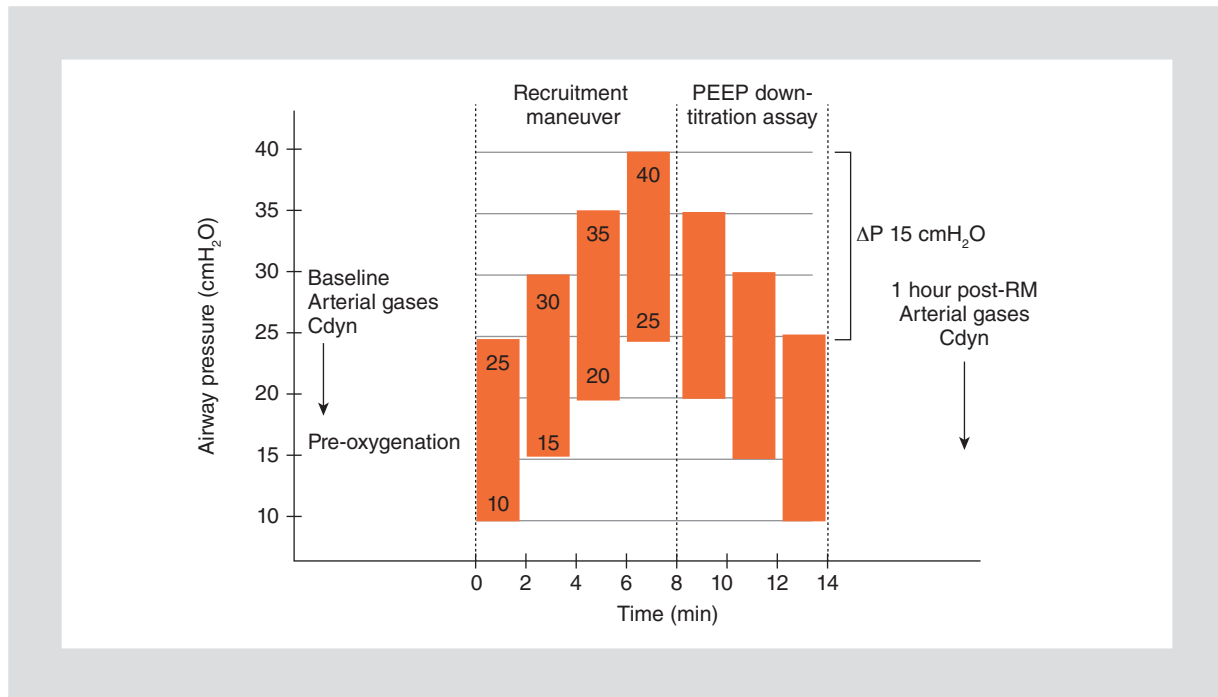


Figure 3. Alveolar recruitment and PEEP down-titration assay protocol. This strategy is carried out under the pressure control modality. It is started with 10 cm H₂O PEEP maintaining distension pressure steady at 15 cm H₂O. The recruitment maneuver is performed sequentially by increasing the PEEP 5 cm H₂O every 2 min until a 25 cm H₂O PEEP is reached. PEEP titration is based on gasometry and lung mechanics. RM: recruitment maneuver (modified from Cruces et al.³³).

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_{dyn} 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_{dyn} 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 H₂O above this inflection point, selecting the most safe and efficacious individual PEEP/ V_T 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_{TP} 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_{TP} 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 Lukenheimer^{42,43}. 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 (ΔP) 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 CO₂ sweeping.

Oxygenation is achieved by increasing the used MAP and FiO₂. Then, according to the oxygenation

goal, MAP is progressively increased while allowing for a parallel decrease of the delivered FiO_2 levels. If necessary, an ARM can be performed by applying 40 cm H_2O over 40 s (oscillator in the off position).

Alveolar ventilation (VCO_2) is a function of oscillation frequency (f) and squared tidal volume ($\text{VCO}_2 = f \times V_T^2$)^{44,45}; consequently, most CO_2 elimination is achieved mainly by increasing the V_T . By widening the oscillation magnitude (ΔP), V_T 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 V_T delivered and the lowest recommended frequency, since its reduction allows for wider oscillation of the piston (increase in V_T), which enables for higher CO_2 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 H_2O , with a progressive increase of the oxygenation index ($\text{OI} = 100 \times \text{MAP} \times \text{FiO}_2/\text{PaO}_2$)⁴⁶. The use of HFOV should be considered in case of:

- Conventional MV failure, either when oxygenation goals are not achieved without exceeding safe P_{plat} and V_T levels ($\text{OI} > 16$) 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 OSCILLATE⁴⁹. 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 V_T 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 ago^{51,52}. This modality is cycled by time and limited by pressure. It is characterized by a high level of continuous airway positive pressure (P_{high}), where periodic releases of this pressure are applied at a lower level of airway pressure (P_{low}). 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 P_{high} and P_{low} have been employed (Fig. 4). Periodical releases provide with a back-up V_T that, together with respiratory rate, enable ventilation, whereas the P_{high} period results in lung recruitment and effective oxygenation. Caution should be used with potential overdistension caused by spontaneous breathing (negative pleural pressure) during the P_{high} stage, as well as also with derecruitment (atelectrauma) that can occur if the P_{low} 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 juxtadiaphragmatic-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 reports^{56,57}. 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.

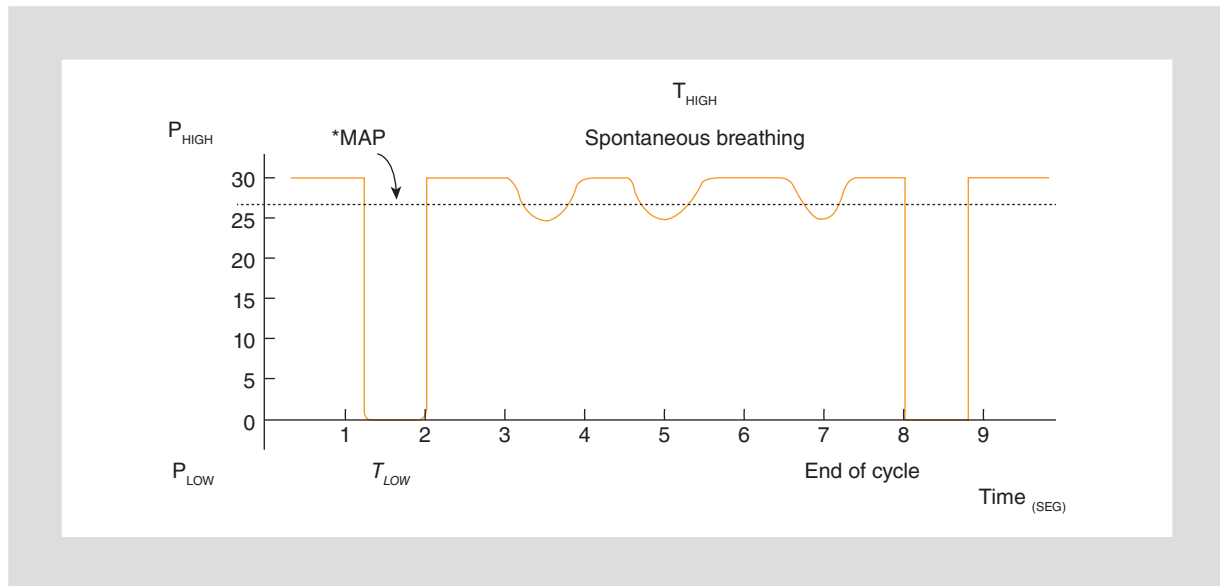


Figure 4. Shapes of the APRV wave with spontaneous breathing. Unlike other MV modes, the trigger (time) (*) starts a fall of the airway pressure (deflated). The amount of pressure change will be the limit. End of the cycle occurs time-wise. Then, airway pressure returns to baseline or mean airway pressure (inflated). P: airway pressure (cm H₂O); T: time (seconds).

Pronation

Currently, this maneuver is widely used⁵⁹. 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^{59,60} (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 atelectatic 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%^{61,62}. In our casuistry, 72 h constitutes an effective and safe “dose”⁶³. A prospective study in adults describes a “time-dependent” gas exchange, intrapulmonary shunt and extravascular lung water improvement with 18 h in the prone position⁶⁴. 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)⁶⁵.

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 hypoxemia⁶⁶.

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^{67,68}. 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 biotrauma⁶⁹, which can be supported by the smaller number of organ failures in groups receiving neuromuscular blockade⁶⁷.

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 hyperglycemia⁷⁰. 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.

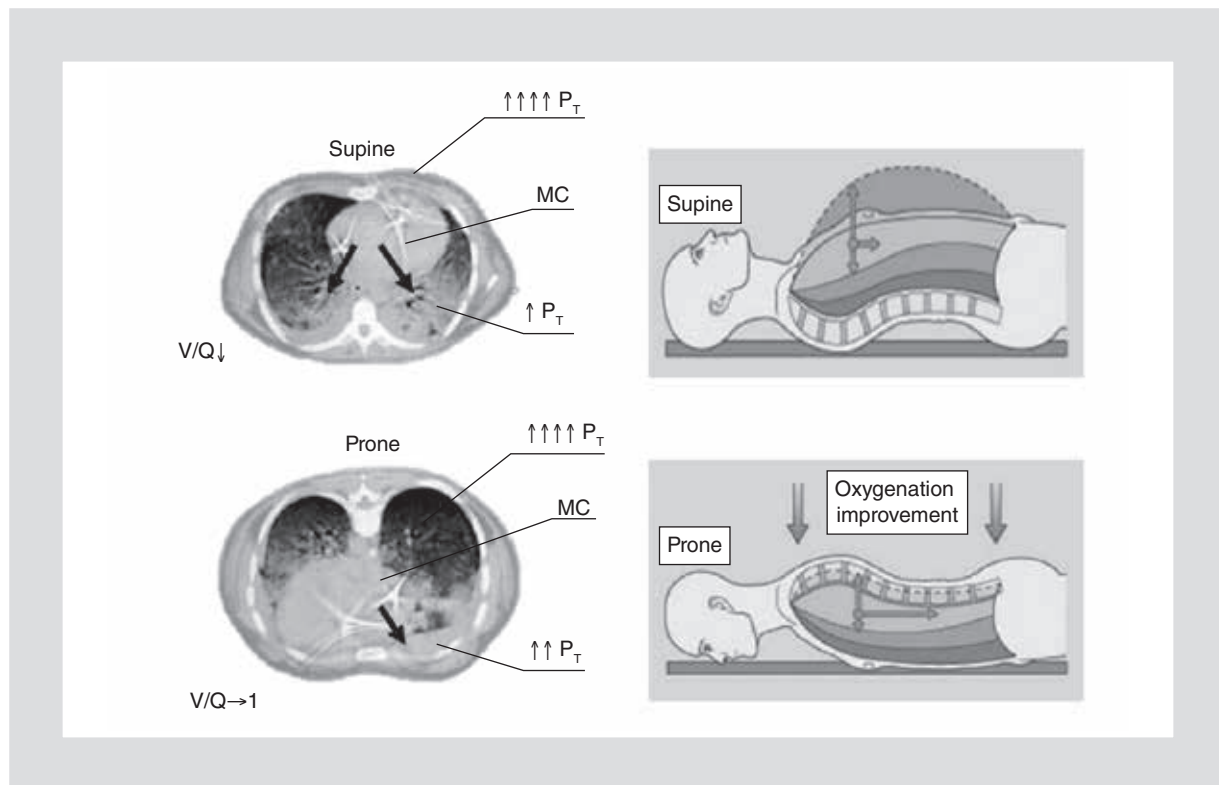


Figure 5. Changes in transpulmonary pressure and perfusion distribution produced by the prone position. CM, cardiac mass weight; P_T , transpulmonary pressure; V/Q, ventilation/perfusion ratio.

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 occasionally 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.

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