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Ventilator-induced lung injury in preterm infants

Lesão pulmonar induzida pela ventilação em recém-nascidos prematuros

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ABSTRACT

In preterm infants, the need for intubation and mechanical ventilation is associated with ventilator-induced lung injuries and subsequent bronchopulmonary dysplasia. The aim of the present review was to improve the understanding of the mechanisms of injury that involve cytokine-mediated inflammation to contribute to the development of new preventive strategies. Relevant articles were retrieved from the PubMed database using the search terms "ventilator-induced lung injury preterm", "continuous positive airway pressure", "preterm", and "bronchopulmonary dysplasia". The resulting data and other relevant information were divided into several topics to ensure a thorough, critical view of ventilation-induced lung injury and its consequences in preterm infants. The role of pro-inflammatory cytokines (particularly interleukins 6 and 8 and tumor necrosis factor alpha) as mediators of lung injury was assessed. Evidence from studies conducted with animals and human newborns is described. This evidence shows that brief periods of mechanical ventilation is sufficient to induce the release of pro-inflammatory cytokines. Other forms of mechanical and non-invasive ventilation were also analyzed as protective alternatives to conventional mechanical ventilation. It was concluded that non-invasive ventilation, intubation followed by early surfactant administration and quick extubation for nasal continuous positive airway pressure, and strategies that regulate tidal volume and avoid volutrauma (such as volume guarantee ventilation) protect against ventilator-induced lung injury in preterm infants.

Keywords: Infant, preterm; Respiration, artificial; Cytokines; Bronchopulmonary dysplasia; Continuous positive airway pressure; Ventilator-induced lung injury

INTRODUCTION

Many preterm infants with signs of early respiratory distress or hyaline membrane disease respond well to exogenous surfactant replacement; nonetheless, these newborns may progress quickly into respiratory failure and require invasive mechanical ventilation (MV). The need for intubation and positive pressure ventilation is associated with so-called ventilator-induced lung injury (VILI). In turn, bronchopulmonary dysplasia (BPD) is directly correlated with the occurrence of VILI in preterm infants. Premature infants are most vulnerable to VILI in the period immediately following birth because their lungs are partially filled with amniotic fluid, they are not uniformly ventilated, and their surfactant content is often deficient.

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BPD is a frequent occurrence in premature infants with extremely low birth weight; its incidence varies from 30 to 75% among newborns with birth weight <1,000g. The diagnostic criteria for BPD are well established,[1] and its long-term consequences include chronic lung disease persisting into adulthood, increased susceptibility to respiratory infections, asthma, pulmonary hypertension, frequent hospital admissions, neurodevelopmental delays, and higher mortality. All of these factors exert a significant economic impact on healthcare systems.

The aim of the present study was to perform a literature review of the mechanisms that lead to VILI and BPD secondarily.

We conducted a non-systematic review in the PubMed database, including only neonatology articles published in the last 10 years. The search terms included the following: "ventilator-induced lung injury preterm", which returned 581 citations; "continuous positive airway pressure" and "preterm", which located 355 classic studies on nasal continuous positive airway pressure (NCPAP); and "bronchopulmonary dysplasia and preterm", which returned 1,065 studies, 139 of which included CPAP and/or MV. First, the titles and abstracts available on PubMed were reviewed, and the articles that did not address the neonatal period and those that only addressed BPD were excluded. As a result, 100 articles that described experimental or clinical studies (mainly those that addressed ventilator-induced lung injury and preterm) were selected. Some historical references located in those studies were included in the review, which was divided into topics to make the understanding of the target subject easier. Articles from groups with proven expertise in neonatal respiratory diseases were retained in the final review.

Inflammation at the origin of chronic pulmonary disease in premature infants

The respiratory system of preterm infants is particularly susceptible to VILI because of specific characteristics such as the reduced amount of collagen and elastin and the reduced functional residual capacity (FRC) caused by the quantitative and qualitative abnormalities of the pulmonary surfactant.[2] Because the branching and expansion of air spaces for sacculi formation, mesenchymal thinning, and surfactant synthesis by type II cells occur late in pregnancy, any damage that occurs in the early stages of lung growth might affect those phenomena, resulting in long-lasting consequences. In addition, inflammation may be associated with abnormal vascular growth, thus damaging the infant's distal airways.

The combination of shear stress, inspiratory volume, air pressure, and high oxygen concentrations damages the respiratory epithelial cells. Protein extravasation into the airways occurs, which inhibits the surfactant function and increases the infiltration of inflammatory cells, such as neutrophils. In addition, MV may induce a systemic inflammatory response involving the activation of the phagocytes in the circulation as well as CD4 and CD8 T cells, thus stimulating the production of inflammatory mediators.[3]

Pro-inflammatory cytokines

Cytokines participate in the pathogenesis of several diseases with their ability to induce the release of other inflammatory mediators, recruit neutrophils, and increase vascular permeability. Pro-inflammatory cytokines are involved in the pathogenesis of practically all the pathological conditions affecting premature infants, especially those affecting the central nervous system, intestines, and lungs. Increased cytokine levels have been demonstrated in sepsis and in moderate-to-severe cases of BPD.[4]

Pro-inflammatory cytokines trigger transcription programs in several cell types that do not respond immediately to the initial insult and thus magnify and prolong the inflammatory response. Cytokines also attract inflammatory cells to the injury site by up-regulating the expression of intracellular adhesion molecules (ICAM)[5] and vascular cell adhesion molecules (VCAM).

Inflammation exerts a direct impact on the integrity of the local tissue and involves a large number of key mediators, regardless of its cause. Interleukin-6 (IL-6), IL-1β, and tumor necrosis factor alpha (TNF-α) are three acute-phase cytokines that are expressed immediately after lung injury occurs. There is an increased local expression of IL-8, a chemokine that attracts neutrophils to inflammatory sites, especially in newborn infants with BPD.[6]

Time pattern of cytokine release in VILI

Following lung injury, the expression of anti-inflammatory cytokine IL-10 is triggered later than IL-8.[7] The production of regulatory interleukins such as IL-10 may be deficient in premature infants, who are thus particularly predisposed to a greater and/or exacerbated inflammatory response.[8]

The pathophysiological interaction between lung development and inflammation was investigated in animal models. Intra-amniotic endotoxin administration to premature sheep altered the expression of the vascular endothelial growth factor (VEGF) with associated vascular remodeling, which allegedly precedes alveolar simplification.[9] Studies of adults and in vitro studies showed that alveolar distension induces a pro-inflammatory response by itself, resulting in increased expression of IL-1β, IL-6, IL-8, and TNF-α, that possibly contributes to the pathogenesis of dysplasia.[10] Alisson et al.[11] showed that in utero ventilation per se promotes significant changes in lung development.

Transforming growth factor beta (TGF-β) was elevated in the bronchoalveolar lavage fluid of newborn infants who developed BPD.[12] The potential relevance of TGF-β as a therapeutic target in BPD was emphasized in a study conducted with rats. The results showed that the use of TGF-β-neutralizing antibodies in lung injuries induced by high oxygen concentrations improved alveologenesis, extracellular matrix assembly, and microvascular development, thus restoring the normal development of the lungs.[13] Similarly, antibodies directed against specific neutrophil chemokines in rats exposed to high oxygen concentrations were able to preserve the normal development of the lungs. That finding is consistent with the result in long-term benefits for newborn infants with pulmonary injuries.[14]

There is controversy in the literature as to the exact moment at which these cytokines are released during the inflammatory response in the lung. Quinn et al.[15] exposed adult rats to two hours of MV and found that the IL-8 levels in the bronchoalveolar lavage fluid from those animals were the same compared to the controls. However, those levels exhibited a remarkable increase four hours later, which suggests that cytokines were expressed in the bronchoalveolar lavage fluid later. In a study by Hillman et al.[16] using lambs, a brief 15-minute period of ventilation resulted in increased cytokine levels in the lungs. According to Capoluongo et al.,[17] the serum cytokine levels of premature newborns subjected to high frequency oscillatory ventilation were lower on days one, three, and five compared with levels in the newborns subjected to synchronized intermittent mandatory ventilation. In adults with no history of lung disease, exposure to one hour of MV was not associated with changes in the levels of inflammatory mediators.[18]

The studies that investigated ventilator-associated systemic inflammation in very small premature infants had very small samples and tested a small number of inflammatory mediators. One study conducted by our research group[19] with full-term and late preterm infants showed that when MV was the only stimulus applied over a short period of time, it induced the release of pro-inflammatory cytokines (IL-6, IL-8, and TNF-α) in the plasma two hours after MV, suggesting that the cascade resulting in lung inflammation and remodeling might start within two hours of intubation in newborn infants. In that study, the IL-10 levels were significantly reduced two hours after exposure to MV. Therefore, in this study - as well as in another study that has not yet been published - we found that activating and deactivating cytokines were co-expressed. It is worth highlighting the recent finding that low IL-10 levels were associated with BPD in premature infants.[8] Those findings support the use of strategies that avoid intubation and positive pressure ventilation whenever possible, even though this goal is difficult to achieve in the case of extremely premature infants.

Other related injury mechanisms

Premature infants often need help to start breathing because residual amniotic fluid and surfactant deficiency may hinder the establishment of FRC. The use of MV to establish FRC might worse the lung conditions through the same mechanisms of aggression as described above, including capillary endothelium, alveolar epithelium, and basal membrane damage, resulting in fluid, protein, and blood extravasation into the airways, alveoli, and pulmonary interstitium, with consequent surfactant inhibition and activation of local and systemic inflammatory responses.[20]

The known direct mechanisms of MV-associated aggression are barotrauma, volutrauma, atelectrauma, and more recently, biotrauma.

Barotrauma occurs when high pressures are used in ventilation, thus increasing the risk of air leak syndromes, such as interstitial emphysema, pneumothorax, and pneumomediastinum, which in turn activate the inflammatory cascade. In newborn infants, MV is usually time-cycled and pressure-limited, but the volume of gas supplied to the lungs is not controlled. However, some studies conducted with animals showed that lung injury is caused by changes in lung volume rather than by the pressure generated inside the airways.[21]

Volutrauma alludes to inadequate lung inflation caused by localized or generalized hyperexpansion of the lung parenchyma. Lungs are injured when they are

inflated to a volume larger than the total lung capacity because of the structural damage caused by stretching, the migration of leukocytes to the lungs, the increase in capillary permeability in the lungs, and interstitial and alveolar edema. However, volutrauma might also occur with lower tidal volumes (Vt) that overdistend the ventilated portions of a partially collapsed lung. An overdistension-induced injury promotes the production of lung cytokines, including IL-6 and IL-8, as shown in a study conducted with lambs[22] subjected to high Vt for a short period of time followed by Vt closer to the normal physiological level; the cytokine levels were lower with the lower Vt. In newborn infants, an overdistension-induced injury may appear after just a few inflations with high Vt and after periods as short as 30 minutes, which indicates the importance of performing resuscitation in the delivery room with appropriate positive end-expiratory pressure (PEEP).[23]

Atelectrauma results from regionally or totally reduced lung parenchyma expansion. Pulmonary injury is associated with alveolar instability: the successive collapsing and reopening of the alveolar walls cause the lysis of the structural elements that compose the lung interstitium, triggering local and systemic inflammation. Experimental models of surfactant deficiency showed that low-volume MV induces cytokine release and initiates the inflammatory cascade, which also occurs in volutrauma.[24]

Biotrauma results from the release of inflammatory mediators secondary to injuries caused by volutrauma or atelectrauma, magnifying the initial mechanical injury and also causing damage in distant organs.[25] The presence of a lung injury increases the number of inflammatory cells and mediators in systemic circulation and also favors bacterial translocation and the release of endotoxins into the air space, which aggravates lung inflammation.

Therefore, MV promotes inflammation and direct damage to the lungs in premature infants. For that reason, strategies for preventing ventilator-induced injuries are needed.

Lung damage prevention

Studies in animals indicate that MV-related lung inflammation is associated with long-term respiratory morbidity.[11,26,27] The use of high Vt without PEEP increased the cytokine concentration in the lungs of rats.[26]One study applied sustained lung inflation (SI) before MV to improve the recruitment and establishment of FRC in lambs and found that SI alone sufficed to increase the levels of pro-inflammatory cytokines.[27] Gentle MV of newborn lambs, even when applied for short periods of time, induced neutrophil recruitment to the lungs, the expression of pro-inflammatory cytokines and dysplasia-like morphologic changes in the lungs.[11] Those findings, together with others in human newborn infants,[19] justify the search for alternative modalities of ventilation, such as non-invasive ventilation and the early use of CPAP in delivery rooms. Those strategies showed promising results for preventing MV-induced injuries in extremely premature infants.[28,29]

NON-INVASIVE VENTILATION FOR LUNG INJURY PREVENTION

Nasal CPAP

Although data reported by the NEOCOSUR network[30] did not show a reduction in BPD rates, the use of NCPAP facilitates the onset of spontaneous breathing, maintains alveolar recruitment with continuous positive pressure, and reduces the use of MV in premature infants. Some epidemiological studies showed that replacing MV with NCPAP was associated with BPD reduction.[31,32] Therefore, there is renewed interest in the use of NCPAP to facilitate the onset of spontaneous breathing and to reduce MV in preterm infants.

The early use of NCPAP is easy to apply.[33] Nasal continuous positive airway pressure reduces the need for MV, and it is also frequently employed to facilitate extubation and to treat apnea of prematurity. One large clinical study randomized 610 infants born at 25 to 28 weeks in the delivery room to receive early NCPAP or intubation plus MV in the fifth minute of life (COIN study). The results did not indicate a reduction in the incidence of BPD nor mortality in the NCPAP group.[28] When NCPAP was applied in the acute stage of respiratory distress, the length of oxygen dependence and ventilation decreased.

Surfactant may be effectively administered to newborns under NCPAP by means of a brief period of intubation followed by rapid extubation to NCPAP. This procedure is known as INSURE (IN: intubation, SUR: surfactant, and E: extubation) and aims at reducing exposure to MV among patients who require exogenous surfactant administration to treat severe early respiratory distress. A meta-analysis published in 2007[34] compared

early INSURE to late surfactant administration and continuous MV and found that the former was associated with reduced need for later MV, lower incidence of BPD, and lower rates of air leak syndromes. Therefore, intubation followed by early surfactant administration followed by fast extubation to NCPAP is protective against MV-induced lung injury.

The pathophysiological mechanisms underlying the beneficial effects of CPAP have not yet been elucidated. It is believed that the low observed rates of BPD are merely due to the avoidance of aggressive ventilation with high Vt and inadvertent hyperventilation.

The effects of CPAP on lung inflammation have been shown only in animals, and the experimental data are controversial. In one study, premature lambs subjected to tracheal CPAP exhibited a slight reduction in cytokine levels compared with those subjected to MV.[35] In contrast, in an experimental study that induced acute inflammation by means of intratracheal lipopolysaccharide, Polglase et al.[36] found that CPAP did not decrease inflammatory markers relative to conventional MV, pointing to a limitation in the use of CPAP when infectious injury is added to immature lungs. That study assessed tracheal CPAP instead of nasal CPAP, which enables speculation that continuous positive pressure in the trachea exerts a direct inflammatory action on the lung, resulting in increased levels of pro-inflammatory cytokines.

In one study conducted by our research group, premature infants born at 28 to 35 weeks of gestational age exhibiting moderate early respiratory distress were subjected within the first six hours of life to NCPAP as the initial modality of ventilation. The results indicated significantly lower levels of pro-inflammatory cytokines two hours after the onset of CPAP, showing that the investigated procedure protected against VILI (non-published data).

Some premature infants subjected to early CPAP develop respiratory failure because of progression of the underlying lung disease, apnea of prematurity, or progressive atelectasis. The rate of extubation failure with CPAP is 25 to 40% in low birth weight infants.[37] New techniques for surfactant administration under CPAP without tracheal intubation are currently being implemented (minimally invasive surfactant therapy - MIST) successfully.[38] Nasal intermittent positive pressure ventilation (NIPPV) is another alternative that is currently being investigated to avoid intubation in some infants.

NASAL INTERMITTENT POSITIVE PRESSURE VENTILATION

The use of NIPPV is quite well established for several pediatric and adult conditions. It is usually performed using masks or prongs, which may be short or long, inserted in one or both nares, being synchronized or not with the infant's inspirations. This ventilation modality is also known as CPAP with peak pressure, nasopharyngeal-synchronized intermittent mandatory ventilation (NP-SIMV), and nasal bi-level positive pressure ventilation (N-BiPAP).[39]

In the present review, we used the term "nasal intermittent positive pressure ventilation." NIPPV alternates between two pressure levels, modifying the infant's FRC and recruiting unstable alveoli or preventing their collapse by generating Vt with delta pressure between both pressure levels, which reduces the respiratory work. Other hypotheses proposed to account for the effects of NIPPV include an increase in pharyngeal dilation, improvement of the respiratory drive, induction of Head's paradoxical reflex, and an increase in mean airway pressure, which allow for alveolar recruitment and increase the Vt and minute volume.[39]

Two randomized clinical trials showed that early NIPPV reduced the need for intubation within the first 72 hours of life compared with NCPAP. Kugelman et al.[40] found a significant difference favoring NIPPV; however, NIPPV failed in infants with lower birth weights. Subsequently, Sai Sunil Kishore et al.[41] found that the need for MV within 48 hours was significantly lower among the infants in the NIPPV group (13.5 versus 35.9%).

Bhandari et al.[42] assessed synchronized NIPPV and found a lower rate of dysplasia and death in the group treated with NIPPV compared with MV. The impact of NCPAP compared with synchronized NIPPV was assessed in a large retrospective study of premature infants weighing approximately 1,250g. In the subgroup with birth weights from 500 to 750g, NIPPV was associated with reduced incidence of BPD (p=0.01) and the combined outcome of BPD and death (p=0.01) compared with CPAP.[43] Those findings suggest that NIPPV is feasible, effective, and associated with lower rates of dysplasia compared with MV.

According to a Brazilian study in which the measured outcome was the need for MV within the first 72 hours of life, NIPPV is feasible and safe and may induce beneficial effects compared with NCPAP, especially in infants with

birth weight >1,000 g.[44] There are no studies in the literature assessing the effects of early (immediately after birth) and primary (after brief intubation and surfactant administration) non-invasive respiratory support procedures on BPD and long-term outcomes.

One single study assessing pro-inflammatory cytokines in premature infants born at 28 to 35 weeks of gestational age subjected to NCPAP or NIPPV was identified.[45] The results did not indicate differences in the interleukin levels between the groups on days one and seven of life. However, the infants subjected to NIPPV were discharged from the hospital earlier.

OTHER TYPES OF MV AND THEIR EFFECTS ON LUNG INFLAMMATION

High frequency ventilation

High frequency oscillatory ventilation (HFOV) was formulated to avoid the major volume and pressure changes that occur in conventional MV. In theory, it should exhibit greater efficiency in the recruitment of areas with atelectasis, especially in infants with surfactant deficiency. A comparison with conventional MV showed that both modalities are equivalent in terms of mortality and the incidence of periventricular hemorrhage.[46]

Early HFOV is associated with the reduction of cytokine-mediated lung inflammation (i.e., lower average IL-8 values in the HFOV group) compared with pressure support (PSV) plus volume guarantee (VGV) ventilation in premature infants with early respiratory distress.[47]

New types of protective MV

Pressure-limited ventilation (PLV), which generates a fixed peak inspiratory pressure (PIP), is the modality traditionally used to control the partial pressure of carbon dioxide ($paCO_2$). When that method is used, the Vt exhibits wide variation. Studies conducted with various types of conventional MV did not find consistent differences about BPD and mortality.[48] Several centers use synchronized conventional mechanical ventilation (SIMV) with low inspiratory pressures to achieve gentle ventilation in newborn infants within local constraints. However, controlled Vt rather than PIP seems a more reasonable strategy for MV in premature infants.

Volume-target ventilation (VTV) affords constant Vt in each inflation and thus reduces the risk of volutrauma. One systematic review[49] compared VTV and PLV in 556 premature infants and found that the first was associated with a significant reduction in the combined outcome of BPD and death but the reduction in BPD alone exhibited borderline statistical significance.

Volume guarantee ventilation (VGV) is a volume-controlled, time- or flow-cycled, pressure-limited modality that measures the exhaled Vt of each ventilator breath and automatically adjusts PIP to deliver the set Vt. VGV is currently used in 80% of the tertiary intensive care units (ICUs) in Australia and in the European countries that use PLV.[50] The ventilator analyzes the Vt of a previous inflation using the expiratory flow to detect leaks and then adjusts the pressure and delivers the set Vt. By controlling the exhaled Vt, VGV is less influenced by endotracheal tube leaks and thus can be used with an endotracheal tube leak up to 50%. With the improvement of the newborn's lung compliance, the PIP required to supply the target volume decreases and the ventilator pressure comes down, which is known as self-weaning.

The effect of these ventilation modalities on cytokine-mediated lung inflammation has not yet been reported.

COMMENTS

Non-invasive ventilation techniques are not new, but they seem promising because they are associated with a lower inflammatory response and seem to play a protective role against lung injury.

Intubation followed by early surfactant administration and rapid extubation to NCPAP protects against ventilator-induced lung injuries in premature infants. The strategies that control the tidal volume and thus prevent the occurrence of volutrauma - volume-controlled ventilation, especially volume guarantee - seem to reduce the rates of bronchopulmonary dysplasia.

The improved understanding of the mechanisms underlying lung injuries involving cytokine-mediated inflammation enables the development of novel protective strategies - small steps in the study of the factors associated with the prevention of bronchopulmonary dysplasia.

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RESUMO

A necessidade de intubação e do uso de ventilação mecânica na prematuridade está relacionada à chamada lesão pulmonar induzida pela ventilação e à consequente displasia broncopulmonar. Busca-se a melhor compreensão dos mecanismos de lesão envolvendo resposta inflamatória mediada pelas citocinas para o desenvolvimento de novas estratégias protetoras. Pesquisou-se na base de dados PubMed, incluindo artigos relevantes, os unitermos "*ventilator induced lung injury preterm", "continuous positive airway pressure", "preterm*" e "*bronchopulmonary dysplasia*". Dados e informações significativas foram compilados em tópicos, com o objetivo de formar uma visão crítica e plena acerca da lesão induzida pela ventilação e de suas consequências ao prematuro. Foi revisado o papel das citocinas pró-inflamatórias como mediadores da lesão, especialmente interleucinas 6 e 8, e fator de necrose tumoral alfa. Foram apresentadas evidências em estudos com animais e também em humanos, mostrando que breves períodos de ventilação mecânica são suficientes para a liberação dessas interleucinas inflamatórias. Também foram revisadas outras formas de ventilação mecânica e de ventilação não invasiva, como alternativas protetoras aos modos convencionais. Concluiu-se que o uso de ventilação não invasiva, a intubação com administração precoce de surfactante e a extubação rápida para CPAP nasal, além de estratégias que regulam o volume corrente evitando o volutrauma (como a ventilação com volume garantido), são medidas protetoras da lesão pulmonar induzida pela ventilação mecânica no prematuro.

Descritores: Prematuro; Respiração artificial; Citocinas; Displasia broncopulmonar; Pressão positiva contínua nas vias aéreas; Lesão pulmonar induzida por ventilação mecânica

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